Hindawi
Journal of Nanomaterials
Volume 2022, Article ID 4155729, 25 pages
https://doi.org/10.1155/2022/4155729

Review Article

Nanomaterials: A Promising Therapeutic Approach for Cardiovascular Diseases

Hitesh Chopra,[1] **Shabana Bibi**,[2,3] **Awdhesh Kumar Mishra**,[4] **Vineet Tirth**,[5,6] **Sree Vandana Yerramsetty**,[7] **Sree Varshini Murali**,[7] **Syed Umair Ahmad**,[8] **Yugal Kishore Mohanta**,[9] **Mohamed S. Attia**,[10] **Ali Algahtani**,[5,6] **Fahadul Islam**,[11] **Abdul Hayee**,[12] **Saiful Islam**,[13] **Atif Amin Baig**,[14] **and Talha Bin Emran**[15]

[1]*Chitkara College of Pharmacy, Chitkara University, Punjab 140401, India*
[2]*Yunnan Herbal Laboratory, College of Ecology and Environmental Sciences, Yunnan University, Kunming, 650091 Yunnan, China*
[3]*The International Joint Research Center for Sustainable Utilization of Cordyceps Bioresources in China and Southeast Asia, Yunnan University, Kunming, 650091 Yunnan, China*
[4]*Department of Biotechnology, Yeungnam University, Gyeongsan, Gyeongsangbuk-do, Republic of Korea*
[5]*Mechanical Engineering Department, College of Engineering, King Khalid University, Abha, 61421 Asir, Saudi Arabia*
[6]*Research Center for Advanced Materials Science (RCAMS), King Khalid University, Guraiger, Abha, 61413 Asir, P.O. Box No. 9004, Saudi Arabia*
[7]*Department of Chemical and Biotechnology, SASTRA Deemed University, Thanjavur, Tamil Nadu 613402, India*
[8]*Department of Bioinformatics, Hazara University, Mansehra, Pakistan*
[9]*Department of Applied Biology, University of Science and Technology Meghalaya, Ri-Bhoi 793101, India*
[10]*Department of Pharmaceutics, Faculty of Pharmacy, Zagazig University, Zagazig 44519, Egypt*
[11]*Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, Dhaka 1207, Bangladesh*
[12]*Department of Immunology, Faculty of Medicine, Academic Assembly, University of Toyama, Toyama, Japan*
[13]*Civil Engineering Department, College of Engineering, King Khalid University, Abha, 61421 Asir, Saudi Arabia*
[14]*Unit of Biochemistry, Faculty of Medicine, Universiti Sultan Zainal Abidin, Malaysia*
[15]*Department of Pharmacy, BGC Trust University Bangladesh, Chittagong 4381, Bangladesh*

Correspondence should be addressed to Atif Amin Baig; atifameen01@gmail.com and Talha Bin Emran; talhabmb@gmail.com

Received 22 January 2022; Accepted 5 February 2022; Published 23 February 2022

Academic Editor: N Senthilkumar

Cardiovascular diseases (CVDs) are a primary cause of death globally. A few classic and hybrid treatments exist to treat CVDs. However, they lack in both safety and effectiveness. Thus, innovative nanomaterials for disease diagnosis and treatment are urgently required. The tiny size of nanomaterials allows them to reach more areas of the heart and arteries, making them ideal for CVDs. Atherosclerosis causes arterial stenosis and reduced blood flow. The most common treatment is medication and surgery to stabilize the disease. Nanotechnologies are crucial in treating vascular disease. Nanomaterials may be able to deliver medications to lesion sites after being infused into the circulation. Newer point-of-care devices have also been considered together with nanomaterials. For example, this study will look at the use of nanomaterials in imaging, diagnosing, and treating CVDs.

1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of death worldwide. CVD was responsible for the deaths of around 18.6 million persons globally in 2019 [1]. Heart disease and related disorders, such as atherosclerosis, arrhythmia, coronary heart disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein

thrombosis, and pulmonary embolism, are all caused by changes in the normal functioning of the heart and its associated structures. The major explanation for these reported ailments is a sedentary lifestyle of living with little or no physical exercise, which has been identified as the leading cause of the CVD in humans. Moreover, the lockdown and work-from-home lifestyle have minimized physical movement, adding more to the sedentary lifestyle. However, various options are available for preventing and treating CVDs, such as regular exercise and physical activity to reduce CVDs [2]. Other factors aggregating the CVDs include smoking, hypertension, and hyperlipidemia. However, exercising can minimize CVD and help reduce the body mass index to normal [3, 4]. Traditional treatment options include operating the affected part for thrombosis and placing the artificial pacemaker for arrhythmia. However, they were adequate to some extent of the population, but they are associated with lower patient compliance, including discomfort for a lifetime. Then, the role of nanotechnology comes into the limelight. Owing to their small size, they can easily be penetrated inside the tight junctions. Due to the small size, the surface area of entities increased, thus providing more comprehensive options for surface modification and binding. The knowledge and utilization of innovative technology shall provide a safe and effective platform for the controlled, targeted delivery of actives that shall lower the incidences of lipid disorders and other diseases [5]. Nanomaterials showed the way forward to overcome the limits arising from using conventional biomaterials [6, 7]. Moreover, new technologies can be coupled with nanotechnology that will revolutionize the treatment of CVDs. Many researchers had prepared nanomaterials mimicking the extracellular matrix and accelerating the healing mechanism [8–10]. The final value of nanoparticulate imaging media is determined by their pharmacokinetics and biodistribution. To provide therapeutically effective tissue imaging, particles must accumulate in target tissues quickly, with little nonspecific uptake. Importantly, these pharmacokinetic requirements for image generation vary by modality. Particles may cause false-positive detection in ultrasensitive modes. Small changes in nanoparticle (NP) size, shape, or surface chemistry may often enhance particle pharmacokinetics, but at a cost. For example, polyethylene glycol is often added to NP surfaces to enhance circulation [11]. This speeds up molecule binding and therapeutic delivery but delays image collecting and bioelimination. Amplification of background signals by larger particles with lower renal clearance [12]. Making nanoparticulate imaging agents safe and effective may be tricky. Longer circulation times and slower tissue absorption rates may need longer decay half-lives, resulting in higher radiation exposure [13–15]. After imaging for 24 hours, diagnostic NPs must be totally removed or biodegraded without producing harm or immunogenicity. Renal filtration is the quickest and most direct way to remove NPs, lowering the danger of biological interactions. Fast renal filtration (4 hours) restricts targeting to certain organs and NP design [16]. Larger nanoparticles are retained in MPS organs until broken down into smaller components and excreted in bile or urine. This method increases exposure due to its slowness and inaccuracy. Larger NPs (250 nm) were cleared quickly in rats, but not in large animals or humans [17]. Organic or iron nanoparticles that can be appropriately eliminated or digested have been authorized by the Food and Drug Administration (FDA) [18]. However, despite their increased extravasation rate, tiny molecules enter tissues more deeply and wash out more rapidly than larger molecules. The endothelium of healthy, nonfenestrated endothelium is often too small to allow considerable extravasation of intermediate-sized NPs, such as those seen in the sinusoidal capillaries of the liver and spleen, as well as those found in tumors and areas of inflammation [19, 20]. For this reason, NPs are more prone to collect in the perivascular gaps of permeable tissues because of their comparatively large size. The enhanced permeability and retention effect (EPR) describes the passive accumulation of NPs in tissues with higher vascular permeability, and it has been used in several medicinal and imaging applications [21, 22]. EPR may be beneficial for detecting pathological tissues, but it is necessary to keep in mind that the effect often occurs over longer time periods (hours) that may not be suitable for clinical diagnostic imaging [20]. Because it generates nonspecific background signals that may obscure or confuse desirable signals from molecular binding events, EPR-based NP accumulation is unfavorable for molecular imaging applications because it inhibits particle removal [12].

Nanomaterials can help in achieving therapeutic functions that are difficult to achieve with traditional biomaterials. Nanomaterials can act as a carrier and can travel through the endothelium of blood vessels also, and they can interfere with the internalization step involved in the delivery of preloaded drugs [23–25]. Developed during the last two decades, there are several distinct types of nanotechnologies for biomedicine with their own distinct features and benefits. Liposomes, NPs, and the application of nanocoating techniques are all considered nanomaterials. The treatment of disease with nanotechnology is currently being concentrated on cancer, specifically on curing and diagnosing cancer. However, it is beginning to move to other treatment areas, specifically to managing CVDs. Current therapies for CVDs are concentrated on restoring normal blood flow through or around the damaged vasculature and the avoidance of repeated cardiovascular shocks. Reduction in subsequent build up and thickness of atherosclerotic plaques, as well as impacts on exterior elastic membranes and fibrous and dense calcium volumes, is obtained by statin treatment [26]. Dual antiplatelet therapy utilizing cyclooxygenase inhibitors such as aspirin and P2Y12 inhibitor such as clopidogrel is first-line treatments for prevention of CVDs, which seek to minimize clot formation and platelet aggregation [27]. There is a necessity for improvement in these therapies, particularly owing to the hazards involved with taking antiplatelet medication having considerably unfavorable side effect profiles, and poor patient compliance [28]. In addition to this, some patients may not react well to antiplatelet medication, which has a detrimental influence on their long-term prognosis. Studies have revealed that individuals who have experienced an acute myocardial infarction but have a poor response to clopidogrel are at greater risk of recurrent cardiovascular events during

follow-up [29]. This underscores the demand for developments in technology and a potential for nanomedicine. This review summarizes the key technologies that are being explored in this field.

2. Why There Is Need for a Nanocardiovascular Targeting Approach

Restoring normal blood flow and preventing repeated cardiovascular shocks are the primary goals of current therapy for CVDs. Statin treatment reduces the growth and thickness of atherosclerotic plaques and the effects on external elastic membranes and fibrous and dense calcium volumes [26]. Aspirin and clopidogrel are first-line antiplatelet medications to prevent cardiovascular disease, which attempt to minimize clot formation and platelet aggregation [27]. It has been reported that administration of clopidogrel and aspirin to minor ischemic stroke patients had a lower risk of major ischemic events in comparison to patients with aspirin alone [30]. It has also been reported that ethidium bromide gets bound to calf thymus DNA signal that indicated clopidogrel bisulphate thus displacing ethidium bromide from its binding site of DNA [31]. Moreover, aspirin, being weaker acid, depresses the availability of clopidogrel bisulphate in basic media [32]. Antiplatelet therapy has high detrimental side effect profiles and low patient compliance, which necessitates improvement in these therapies [33]. In addition, some patients fail to react effectively to antiplatelet medication, which severely impacts their long-term prognosis. Following an acute myocardial infarction, individuals who show limited response to clopidogrel are at greater risk of recurrent cardiovascular events. This finding is consistent with previous research [29]. This demonstrates the need for technological improvements and the potential for nanomedicine.

3. Nanotechnology-Based Approaches

3.1. Liposomes. Liposomes are the uni or multilamellar lipoid membrane carriers that can entrap both hydrophilic and lipophilic drugs for the targeted delivery at distant organs. The spherical shape of the vesicle closely resembles the structure of the cell membrane. Liposomes are biocompatible, biodegradable, and lower the toxicity arising after entrapment [34].

In myocardial infarction, reperfusion is an essential step in restoring the circulation to the ischemic myocardium. An improper way may lead to reperfusion injury, decreased cardiac functioning, and scar formation at last. It is a complex phenomenon and comprises multiplayers such as inflammatory cells and cardiac fibroblasts. Researchers identified some specific peptides for infarct and border zone using the in vivo phage display and optical imaging methods [35]. The cardiomyocytes, endothelial cells, myofibroblasts, and ckit+ cells were present in border zones of remodeled infarcts. Researchers prepared site-specific liposomes, i.e., cardiomyocyte-specific (I-1) liposomes, for the targeted delivery of Poly (ADP-ribose) polymerase-1 inhibitor after myocardial reperfusion. With the use of liposomes, the AZ7379 (PARP-1 (poly [ADP-ribose] polymerase 1) inhibitor) concentration increased in the border zone at 24 h post-administration compared to control AZ7379, freely administered. About a 3-fold increase in inhibitory therapeutic efficiency was observed due to entrapment of PARP-1 inhibitor.

Berberine has also been reported to reduce the negative impact on cardiac functions after myocardial infarction [36]. Formulators developed liposomes using ethanol injection technique using dipalmitoylphosphatidylcholine, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino (polyethylene glycol)-2000] (DSPE-PEG2000), and cholesterol as lipoids and dissolved them in HEPES [(4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid)] buffered saline and berberine. Macrophages infiltrate into the heart during and after infarction and cause inflammation [37]. During this event, the capillary permeability increases. It was hypothesized that encapsulating the liposomes shall enrich the berberine. Berberine in the heart tissue shall help to extravagate by the locally enhanced permeability and thus improve the local delivery and overall treatment. Practically, after intravenous administration, the berberine liposomes got accumulated at infarcted heart tissue after 3 days of myocardial infarction. It was indicating the successful integration of liposomes for delivery to the target site. Moreover, the macrophages infiltrated into infarcted heart tissue, suggesting the release of preloaded berberine at the target site by liposomes and improving the anti-inflammatory response [38–40].

MicroRNA-21 are short regulatory RNA acting as down-regulators for gene expression by inhibiting mRNA translation and promoting mRNA degradation [41]. Many researchers suggested using microRNA (miRNA) in cardiac hypertrophy and other associated cardiac disorders [42, 43]. It has been observed that the expression of levels of mir-21 in cardiac cells gets upregulation with oxygen-glucose deprivation. Depletion of miR-21 causes the enhancement in fibroblast activation and promotes the cardiomyocytes against oxidative stress. Researchers prepared miR-21 liposomes as a promising strategy for treating acute myocardial infarction [44]. The process of liposomes was chosen owing to poor stability and insufficient cellular uptake that acted as a significant hurdle for miR-21. Formulators developed miR-21 mimics into liposomes modified with the cardiac troponin T antibody to target the miR-21 to the myocardium. The liposomes showed enhanced targeting efficiency to hypoxia primary cardiomyocytes. The liposomes were administered via the tail vein and got accumulated inside the ischemic heart. The liposomes improved cardiac functions and a decrease in infarct size after acute myocardial infarction and maintained cardiac cells' viability. Darraji et al. prepared azithromycin's liposomal preparation to reduce its cytotoxicity and enhance its immunotherapeutic efficacy [45].

The liposomes were prepared by using the DSPC (distearoylphosphatidylcholine), DSPG (distearoylphosphatidylglycerol), and cholesterol via the thin-film hydration method. The liposomal formulation showed a reduction in cytotoxicity and mortality rate by 50% in mice. Also, the

liposomes decreased the cardiac inflammatory neutrophils and infiltration of inflammatory monocytes while angiogenesis got enhanced. Wei et al. administered Lipoprostaglandin E1 (Lipo-PGE1) before primary percutaneous coronary intervention (PCI), and improvement in myocardial microcirculation in reperfusion injury was observed [46]. During acute myocardial infarction, damage to the microvascular is observed, limiting the completeness of tissue perfusion [47]. The intravenous administration of Lipo-PGE1 causes a decrease in cTFC (corrected thrombolysis in myocardial infarction frame count) and increased myocardial blush grade. After 6 months of follow-up, it was found that the patients with Lipo-PGE1 have fewer major adverse cardiac events. Atherosclerosis is a disease characterized by the deposition of plaque inside the blood vessels. The extravasation of liposomes to plaque can be carried out using the injured endothelium's enhanced permeability and retention effect in atherosclerosis. The damaged vessels have been found to overexpress some molecules that can target the liposomes and thus permit liposomes' entry. The molecules such as vascular cell adhesion molecule 1 (VCAM1), intercellular adhesion molecule-1 (ICAM-1), P-selectin, E-selectin, and alpha V beta three integrins are generally found at luminal endothelium or newly formed endothelium. Even the noncellular components of plaques could also act as the target for liposomal entry [48].

The clinical trial was conducted with liposomes encapsulating the prednisolone for use in atherosclerosis [49]. The liposomes were found to increase the plasma half-life to 63 hours. The macrophages isolated from iliofemoral plaques showed appearance in 75% of macrophages isolated. However, the liposomes were not able to reduce the arterial wall permeability in infected patients. Later, it was confirmed that liposomal prednisolone showed accumulation in low-density lipoprotein receptor knockout mice. The liposome enhanced the recruitment of monocytes at plaque position [50].

The choice of therapeutic drug for treatment has been under discussion for many years as angiogenesis also constitutes a potential target for the treatment of atherosclerosis [51]. Fumagillin has been shown to possess antiangiogenic effects in tumor therapies [52]. Also, the water-soluble analog of Fumagillin, TNP-470, has been shown to lower plaque growth in the case of atherosclerosis [53]. Pont et al. prepared liposomes of the antiangiogenic drug Fumagillin derived from *Aspergillus fumigatus* [54]. Fumagillin is a selective inhibitor of endothelium cell proliferation and migration. The liposomes consisted of 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC), 1, 2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-7-nitro-2-1, 3-benzoxadiazol-4-yl (DPPE-NBD),1, 2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-biotinyl (DPPE-Biotin), and Tween 80, and the drug was incorporated using the thin-film hydration method. The liposomes were labile, and biotin-phospholipid was attached as conjugation between biotinylated antibodies via Avidin Bridge. An antibody-targeted macrophage scavenger receptor B (CD-36) was attached to the liposome, causing an enhancement in signals from MRI and fluorescence. Also, the CD-36 is being a glycoprotein and is present in membranes of macrophages. Therefore, the anti-CD36 targets the macrophages scavenger receptor B facilitating the *in vivo* imagining in atherosclerosis plaques. The liposomes showed a reduction in plaque development by 23.7%. The liposome administration decreased the fatty streaks that started to appear normal at 8-20 weeks of administration in mice fed with an atherogenic diet. Fluorescence imaging and histochemical analysis reported the accumulation of liposomes. To exploit the role of macrophages, another group prepared liposomes consisted of decoration of phosphatidylserine and DSPE-PEG2000 onto the surface of liposome encapsulating pioglitazone [55]. Pioglitazone is a peroxisome proliferator-activated receptor γ agonist for atherosclerosis macrophages. The surface decorated liposomes showed more penetration efficiency towards activated vascular endothelial monolayers and suppressed the inflammatory cytokines *in vitro*.

Thrombosis is one of the significant contributors to CVDs. Many antithrombosis drugs have been effective but showed lower limited efficacy due to lower shorter half-life in plasma and associated side effects. The liposomes functionalized with cyclic RGD encapsulating urokinase were found to be effective in thrombosis [56].

The liposomes could bind to activated platelets, and the in vitro pattern showed a release plateau in 5 h with 60% release for urokinase. As a result, the dose of urokinase decreased by 75%, as evidenced by the mouse mesenteric thrombosis model. Interleukin-10 (IL10) acts to alleviate the inflammation arising from atherosclerosis plaque, using cRGD conjugated liposomes and IL10 [57]. The liposomes with the size of 180 nm and PDI 0.14 were prepared. The liposome administration *in vitro* showed sustained release of IL10 and reduced the ROS and NO. The IL-1β and TNF-α were downregulated with administration in RAW 264.7 cells apart from drug delivery applications; liposomes have also been utilized in imaging applications. Liposomal nanoparticles were utilized in positron emission tomography (PET) [58]. The liposomal NPs were decorated with Zirconium-89. After 15 days of administration, the positron emission tomography/computed tomography and PET/MRI showed their biodistribution and vessel wall targeting in the rabbit atherosclerosis model. The liposomes showed biodistribution patterns like long-circulating NPs and accumulated in atherosclerosis lesions confirmed by imaging techniques. Many other researches have been tabulated in Table 1.

The main advantage of using liposomes for cardiac applications includes encapsulating and targeting high payload on lipoidal vesicles. However, liposome components' interaction with the immune system has contributed to the difficulties encountered during their translation into therapeutic application. Antibodies may be produced against their different components and/or the enclosed payload when they are subjected to synthetic changes in order to improve their usability as drug delivery vehicles. According to Dams et al. [65], repeated injection of PEGylated liposomes has been related with a loss of their long circulating characteristics and a subsequent clearance from the circulation. The "accelerated blood clearance" (ABC) phenomenon

Table 1: Literature view of liposomal preparation for cardiovascular diseases.

Name of drug/active	Constituents of liposomes	Animal model/ cell lines	Particle size	Outcome of study	References
Ameliorated sirolimus	Dioleoyltrimethylammonium propane (DOTAP), dimyristoylphosphatidylglycerol (DMPG), distearoylphosphatidylethanolamine polyethylene glycol 2000 (DSPE-PEG)	Balloon injured rats	100 nm	As with decrease in size of liposomal vesicles and change in ionic strength resulted in variation in antirestenosis efficacy of liposomes	[59]
Human vascular endothelial growth factor-165	Cholesterol (Chol) + DOTAP liposome (CD liposome)	Rat heart	50-150 nm	It was observed that the liposomes caused a reduction in apoptosis and improvement in angiogenesis. Also, the study showed gene transfection efficiency using cyclodextrin liposomes medicated hVEGF165 gene transfer	[60]
α-Tocopherol	Egg lecithin, cholesterol, sodium deoxycholate	Sprague Dawley rats	231.1 ± 6.1 nm	The hydrogels showed a highly porous structure interconnected throughout and liposomes distributed uniformly. The liposomes showed delayed-release and excellent biocompatibility in cardiomyocytes. The formulation was able to resist oxidative stress and improve the survival of cardiomyocytes	[61]
Indium	Phosphatidylserine and PEG2000; PEG5000	ddY mice	200 nm	The PEGlyated liposomes showed slow uptake in comparison to non-PEGylated liposomes. Also, the in vivo results showed slower blood clearance in PEGylated liposomes	[62]
Atorvastatin calcium and curcumin	Mal-PEG2000-DSPE and cholesterol	ApoE knockout ($ApoE^{-/-}$) mice	190 nm	Targeted liposomes transported atorvastatin calcium and curcumin to defective endothelial cells, leading in synergistic reduction of adhesion molecules (E-selectin and ICAM-1) and plasma lipid levels	[63]
Fluocinolone acetonide	DMPC (1,2-dimyristoyl-sn-glycero-3-phosphocholine), DPPC, and DSPC	Apolipoprotein E-knockout ($ApoE^{-/-}$) mouse model	100 nm	*In vivo* studies carried out with an apolipoprotein E-knockout ($ApoE^{-/-}$) mouse model of atherosclerosis show accumulation of liposomes in atherosclerotic plaques, colocalization with plaque macrophages, and antiatherogenic effect over 3 weeks of treatment	[64]

is the term used to describe these phenomena. When it comes to the therapeutic use of PEGylated formulations that need numerous dosage regimens, the ABC phenomenon is a significant source of worry. Also, these systems have inability to maintain long-term stability, which results in the release of drugs at an inopportune time. In addition, greater excipient-to-drug ratios are often needed, making them costlier and less effective than some of the polymer-based systems available on the market today.

3.2. Nanoparticles (NPs). NPs are characterized by smaller sizes and can be surface functionalized with new side chains. Their smaller size presents a large surface area for interaction and binding. The NPs can permeate easily through the tight junctions, as they can be prepared both as hydrophilic and hydrophobic. NPs can be conjugated with d- and f-block elements and targeted from macrophage scavenger receptors, thus improving the cardiac magnetic resonance that can help diagnose atherosclerosis [66].

Natural agents such as curcumin can also be entrapped inside the NPs and targeted to treat Ehrlich ascites carcinoma cardiac toxicity. The treatment with NPs resulted in a reduction in volume and tumor cells with a marked increase in apoptotic cell numbers in ascites fluid. The treatment also decreased the cardiac markers [67].

Cerium oxide, also known as Ceria, has also been reported to show cardioprotective effects. Pagliari et al. reported the use of Ceria NPs (nanoceria) in controlling the ROS-induced cell damage on the cardiac progenitor cells (CPCs). CPCs are an autologous source of cells and needed

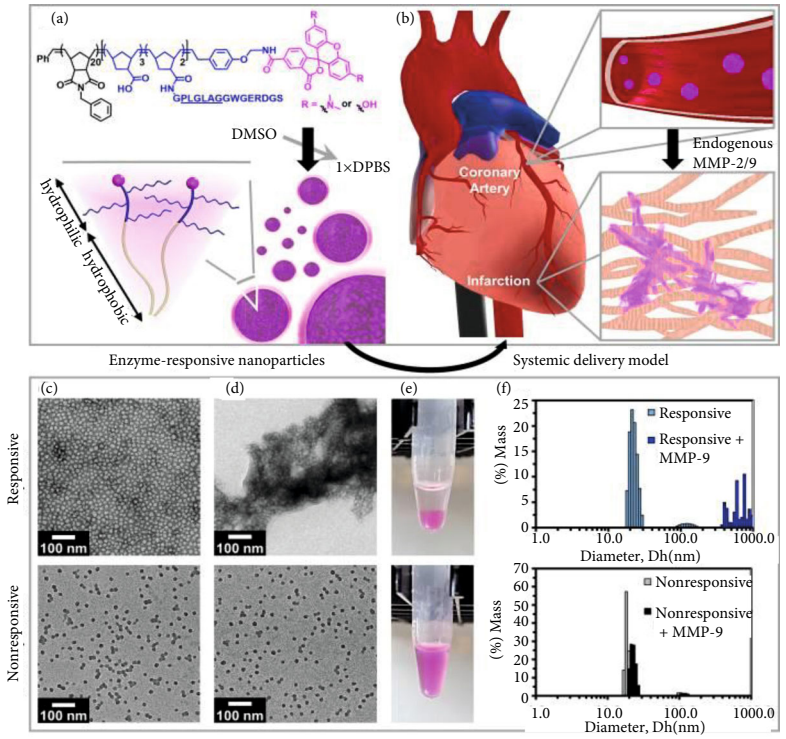

Figure 1: (a) Representation of enzyme responsive nanoparticles for use in myocardial infarction. (b) Representation of nanoparticles freely in the bloodstream and later getting settled at the infarcted vessel. (c) *In vitro*: responsive and nonresponsive nanoparticles. (d) Responsive and nonresponsive behavior of nanoparticles on activation. (e) Images of nanoparticle solution after activation. (f) DLS pattern of nanoparticles after and before activation. Reproduced with permission from reference [73].

microenvironmental conditions for preparing them in *in vitro* conditions. Findings showed that CPCs resident in the heart were quickly exposed to uptake the nanoceria, as they were present in the cytosol. Even after 7 days, no evidence of encapsulation and particle translocation was seen and prevented the progenitor cells from hydrogen peroxide-induced injury and nanoceria acting as an antioxidant [68].

Similarly, mesoporous silica-based nanoparticles prepared showed detection ability for hydrogen peroxide, the selective drug released and controlled treatment toward heart failure. The peroxide sensing probes were functionalized on the surface for detection and captopril as the drug was loaded inside the NP. The hydrogen peroxide present in tissue could react with the probe causing dissociation of cyclodextrin present on the surface, causing drug release at the site. This occurs as a turn-on and turn-off mechanism [69].

Researchers prepared inhalable peptide-based calcium phosphate NPs for the treatment of CVDs [70]. The particles of <50 nm size, with excellent biocompatibility and biodegradability option, allow rapid translocation of NPs from pulmonary system to the bloodstream and heart, where peptides are released. The rodent model and porcine with diabetic cardiomyopathy showed improvement in myocardial contraction, resulting in everyday functioning. However, this approach was based on the pathophysiological conditions of the lungs. Thus, this may affect the persistence of nanoparticles targeted to the myocardium. It has already been reported that macrophages' role in inflammation-related mutations in patients with myocardial infarction [71]. During ischemia, inflammatory macrophages get accumulated in the arterial wall and heart muscles, causing tissue destruction and death. Therefore, there is a need to evaluate the positioning of macrophages to prevent further destruction. Keliher et al. described the use of 18F-Macroflor (modified poly glucose nanoparticles with high avidity for macrophages). Owing to its smaller size, the NP can be excreted renally. Macroflor is enriched in cardiac, and plaque macrophages can direct the PET signals as evidenced in mouse and rabbit atherosclerotic plaques. Positron emission tomography (PET) imaging helps detect the macrophage population, while MRI reports the extent of inflammation [72].

Similarly, Nguyen et al. reported enzyme-responsive NPs for the increased retention and accumulation in the myocardial infarcted heart via IV injection. The NPs were designed to respond to enzymatic stimuli (matrix metalloproteinases), causing the morphological changes in the discrete NPs into network-like scaffolds (Figure 1). The IV administration causes enzyme-responsive NPs to circulate in the bloodstream and reaches the infarcted point in vasculature. At the injured site, NPs were found to remain for about 28 days' postadministration. Reducing the degree of polymerization of hydrophilic block and degree of conjugation of hydrophilic peptides increased the responsiveness of NPs [73].

Table 2: Literature overview of nanoparticle-based study done by other researchers, where n.m. is not mentioned.

Active ingredient	Disease targeted	Type of nanoparticle	Particle size	Outcome of study	References
Atrial natriuretic peptide (ANP)	Ischemic heart disease	Biodegradable porous silicon (PSi) nanoparticle	168-230 nm	ANP-PSi nanoparticles loaded with a unique cardioprotective small molecule attenuate hypertrophic signaling in the endocardium, signifying their cardioprotective potential	[77]
Vascular endothelial growth factor	Ischemic heart disease	Pluronic F-127 (poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) triblock copolymer-based nanoparticles	n.m.	The VEGF-loaded nanoparticles and their gel formulation improved heart functions such as improved ejection fraction and cardiac output	[78]
Exosomes	Ischemic heart disease	Fe3O4 core and a silica shell	200 nm	The introduction of a magnetic field resulted in the accumulation and cleavage of hydrazone bonds between acidic pH of injured cardiac tissue, causing exosomes to release, leading to a reduction in infarct size and improved ejection fraction and angiogenesis	[79]
Atorvastatin and rapamycin	Valvular heart disease	PLGA nanoparticles	99-103 nm	The modified valves showed a reduction in levels of TNF-α levels and increased IL-10. Further results showed resistance of valves to the calcification after implantation due to the release of drugs	[80]
Atrial natriuretic peptide (ANP) and linTT1	Atherosclerotic plaques	Acetylated dextran	100-200 nm	The results demonstrated that the nanosystem has the potential to exploit the "hitchhike" effect on M2-like macrophages and thereby improving the ability of the ANP peptide to target infarcted hear in a dual-targeting strategy	[81]

Vascular endothelial growth factor (VEGF) chemically is a proangiogenic cytokine that promotes neovascularization in patients' hearts with ischemic heart. However, VEGF has a shorter half-life and rapid renal clearance rate. Oduk et al. [74] prepared VEGF-based nanoparticles (average size 113 nm diameter) for repairing the heart after myocardial infarction. The VEGF was encapsulated in the PLGA NPs, and increased the exposure time for VEGF (31 days exposure time), improved cardiac functions (after exposure of 4 weeks), protected the heart against the left ventricular remodeling were its pharmacological actions.

Simdax (levosimendan) is the most common and effective inotropic agent reported for improvement in myocardial contractility in heart failure patients [75]. Spivak et al. conjugated gold nanoparticles with the Simdax to evaluate the targeted delivery of the drug and the effect of sonoporation on nanoparticles [76]. The nanoparticles conjugated with the Simdax were administered to Wistar rats (chosen as a model for heart failure with doxorubicin-induced failure). However, the administration does not induce any changes in the liver, and no ascites were observed. However, the conjugated formulation showed higher hydrothorax reduction, but no significant difference was observed in recovery. Sonoporation enhanced the transfer of gold nanoparticles into the cell, and significant localization was observed in the mitochondria region. The work done by other researchers has been tabulated in Table 2.

A platform for inflammatory macrophage theranostics was developed by Qin et al. using gold nanorods (Au-NRs) [82]. Micro-CT (computed tomography) imaging of macrophages showed that the signal intensity increased with increasing concentration. Au-NRs intravenously injected into Apo E mutant mice elicited a little increase in CT intensity in the inflamed femoral artery. Laser therapy also increased the temperature of the irritated femoral artery by up to 50.5°C (808 nm). In the femoral artery restonosis, CD68-stained histology data demonstrated that macrophages had been damaged. As a novel theranostic platform treating atherosclerosis, this nanosystem seems to be nontoxic and promising. Detection of atherosclerosis might be improved by using computed tomography agents, such as gold. CNR (contrast-to-noise ratio) of Au-NPs is greater than the commercially available iodinated agent Visipaque^{TM} [83]. However, CT imaging equipment itself entails radiation exposure, and numerous scans in a short period of time are unlikely to be therapeutically feasible. Radiation-related harm may be reduced in the future by using more sensitive CT agents. Phosphatidylserine and oxidized cholesterol ester derivative cholesterol-9-carboxynonanoate nanoparticles were synthesized by

Bagalkot et al. to target macrophages of the M1 inflammatory phenotype [84].

This nanosystem also includes gadolinium (Gd) and fluorescein isothiocyanate (FITC) for MRI detection and optical screening. Noninvasive MR imaging of atherosclerotic plaques in $ApoE^{-/-}$ mice was made possible by combining nanoparticles Gd-FITC-LiLa. Inflammatory adipose tissue macrophages might potentially be used as a medicine carrier for them. In order to give a therapeutic anti-inflammatory effect, this nanocarrier was loaded with rosiglitazone (Rosi). Atherosclerosis imaging and treatment might benefit from LiLa NPs, according to the study's findings. A polyacrylic acid-coated magnetic nanoparticle conjugated with rtPA was developed by Ma et al. for use in thrombolysis and thrombosis diagnosis (PAA-MNP-rtPA). While free rtPA demonstrated no appreciable thrombolysis in rat right iliac arteries after 25 minutes of PAA-MNP-rtPA treatment, the 0.2 mg/kg dose of PAA-MNP-rtPA could efficiently dissolve the thrombus [85]. There was no MRI in this trial. MRI contrast agents PAA-MNP-rtPA might be tested in follow-up investigations because of the nanosystem's iron core. When Yang and colleagues synthesized core-shell NPs with Fe3O4 magnetic NPs for thrombolysis, they created a comparable NP [86]. For the breaking of blood clots, the NPs had 276 g of active rtPA per milligram. Magnetic guiding lowered clot disintegration time from 39.2 ± 3.2 to 10.8 ± 4.2 minutes. In rats, this nanosystem's biodistribution was studied using SPECT/computed tomography techniques (CT). The Fe_3O_4-PLGA-rtPA/CS-cRGD NP (Fe_3O_4-PLGA-rtPA/CS-cRGD) was synthesized by Zhou et al. in another study, which included the development of the Fe_3O_4-PLGA-rtPA nanoparticle with a core of rtPA and an outer shell of Fe_3O_4 and poly (lactic-co-glycolic acid) [87]. Fe_3O_4-PLGA-rtPA/CS-cRGD NPs dissolved clots three times faster than free rtPA did after 60 minutes of administration. Researchers found that CS-cRGD coating did not alter the MRI signal, and the NPs displayed a significant T2 signal in the rats' abdomens with thrombus. The precise targeting function of Arg-Gly-Asp (RGD) peptides was critical to the success of therapy and imaging. RGD might bind to active platelets at thrombus sites as a receptor antagonist of platelet membrane glycoprotein GP IIb/IIIa [88].

Using tagged mitochondria, Cowan et al. devised a method of cardioprotection [89]. Iron oxide NPs were used to identify mitochondria such that they could be detected by PET, fluorescence imaging, magnetic resonance imaging (MRI), and micro-CT. As predicted, fluorescence pictures of iron oxide NPs and Fluorine-18-rhodamine 6G are attached to mitochondrial amine groups through transmission electron microscopy. In order to lessen the extent of the infarct, mitochondrial transplantation was employed in the ischemic regions to enhance ATP content in the tissues. The infarct size of the rabbit ischemic hearts was significantly reduced following treatment with these tagged mitochondria. T2-weighted images of the ischemic left ventricle showed a strong signal from 18F-R6G-labeled mitochondria. Signals from the MRI and PET scanners were absent from the typical right ventricle. Infarct size could be reduced, and cell loss could be minimized using this method [90, 91]. This strategy might be used to safeguard the heart. Mitochondria-transplanted hearts exhibited a substantial decrease in infarct size compared to the control group of normal hearts. Iron oxide NPs are the most extensively utilized image contrast agents for magnetic resonance imaging (MRI), which is used to diagnose a variety of CVDs. For MRI and CT, perfluorocarbon and gadolinium NPs, as well as gold nanoparticles, have been developed for the detection of vascular damage and atherosclerosis. Atherosclerosis may also be seen with photoacoustic imaging agents such as copper sulphide, which provide a strong photoacoustic signal. Fluorescent dye and polymer are used in another theranostic device to monitor and evaluate treatment effects in the ex vivo environment. Because the human body has a far greater level of fluorescence than cells or mice, fluorescent drugs are unlikely to be used in clinical studies. Polymeric NPs can change and resorb in the body, making them prominent in cardiovascular nanomedicine. Oral, cutaneous, mucosal, or transdermal delivery of these NPs is possible [92].

PEG, PGA, and PLA are the most often utilized biodegradable polymeric nanocarriers (PLA). They are biodegradable because they are readily excreted as CO_2. PLGA has been widely explored as a CVD medication carrier [93]. Both SB431542 and CHIR99021 (model drugs) were given as dextrancoated nanoparticles to convert fibroblasts into cardiomyocytes. To administer the medicines, AcDX (acetalated dextran) nanoparticles functionalized with spermine were used. It is always attractive to reprogramme myofibroblasts and fibroblasts into healthy myocytes to replace lost cardiac cells [94]. The polymeric NPs containing quercetin increased water solubility and stability. This halted atherosclerosis and to boost medication effectiveness and minimize ROS generation; this antioxidant was encapsulated on PLGA nanoparticles [95]. Polymeric nanocarriers deliver antiproliferative drugs to injured vasculature [96].

ROS plainly damage heart cells and induce thrombosis (e.g., hydrogen peroxide). They have delayed medication release and fast blood circulation. As a consequence, thrombo-occluded vein clots disintegrate faster. These NPs include antioxidant (glutathione) and anticoagulant (heparin) properties. Controlled and targeted medication administration proved efficient in treating vascular disorders in two hours [97].

Quantum dots (QDs) are semiconductor nanocrystals with a 10 nm average diameter. They have varying luminescence qualities depending on their size, as well as different energy levels. There have been recent efforts to create heavy metal-free QDs that are less toxic since QDs have clinical safety restrictions due to the usage of heavy metals that may produce toxicity or other adverse effects [98]. Immunosensors for detecting cardiac myoglobin (cMyo), a significant biomarker for the diagnosis of MI, have been developed by Tuteja and colleagues. An immobilized template of GQDs was created by hydrothermally synthesizing and implanting them on screen-printed electrodes (SPEs). Finally, SPEs were treated with anti-cMyo antibodies to detect cMyo more precisely. Compared to the usual enzyme-linked immunosorbent assay (ELISA) tests,

modified SPEs showed a broad range of 0.01–100 ng mL^{-1} and a detection limit of 0.01 ng mL^{-1} (i.e., more than 400-fold in comparison) [99].

Silica NPs were recently employed to transport adenosine, a prototype cardioprotective drug, into I/R heart tissue [100]. Silica NPs can generate ROS, which can cause cytokine release and apoptosis [101]. IT injection of silica NPs raises hs-CRP levels in rats in a size-dependent way, as well as TNF-a, IL-6, and IL-1 levels. These particles promote inflammation in the cardiovascular system. After being exposed to silica nanoparticles, the levels of ET-1, D-dimer, LDH, and CK-MB rose. Following exposure to these particles, there was an increase in vascular permeability [102]. Another investigation found a small alteration in cell viability and genetic content [103, 104]. When BALB/c mice were given 10 mg/kg polyacrylic acid coated-Fe_2O_3 NPs, their heart rate was reduced acutely [104]. Sun et al. investigated the effect of Fe_2O_3 and Fe_3O_4 NPs (0.001–100 g/mL) on endothelial cells of the heart microvascular. Their findings demonstrated that these particles had no significant effect on plasma membrane permeability or inflammatory markers [102].

Superparamagnetic iron oxide NPs were found in the heart, lung, kidney, liver, and spleen after subcutaneous administration [105]. Iron oxide NPs cause oxidative damage due to ROS production. As a result, cytoskeletal disruption, decreased proliferation, and cell death ensued [106]. On the contrary, using confocal microscopy, it was also observed that negatively charged superparamagnetic iron oxide NPs had no significant effect on the actin cytoskeleton of heart cells while dramatically disrupting the actin cytoskeleton of kidney cells.

3.3. Nanofibers. Nanofibers can be defined as fibers with a small diameter of range 1-1000 nm. The nanofibers can be employed for cardiac tissue engineering and regeneration purpose. Many researchers have combined nanofibers with drug elution or embedded cells for regenerative engineering and treatment of dilated cardiomyopathy. The human inducible pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) were cultured on the cardiac patch using PLGA-based nanofiber scaffolds [107]. The patch showed >90% parallel alignment with ECM of the animal model myocardium and showed more calcium cycling. The high calcium cycling enables the cells to get contracted at a higher frequency. The presence of actinin and connexin-43 confirmed the maturity and terminal differentiation of cardiomyocytes. Another study also confirmed the use of PLGA in seeding embryonic stem cell-derived ventricular cardiomyocytes for regular electrical stimulation and was resistant to arrhythmogenesis [108].

Wu et al. prepared a 3D cellular anisotropic cardiac structure for tissue regeneration. The nanofiber yarn is made of polycaprolactone, silk fibroin, and carbon nanotubes. The yarn enhanced the cardiomyocyte's maturation. The three-dimensional hydrogel provided an environment for endothelialization and shown their potential to be used in 3D cardiac anisotropy [109].

Ischemia causes gradual loss to ECM, after MI causing the heart failure later. To combat this, Lakshamanan et al. prepared a nanofibrous scaffold using poly (l-lactide-co-caprolactone) (PLCL) and poly (2-ethyl-2-oxazoline) (PEOz) via electrospinning technique with a diameter of size 500 nm [110]. Due to the presence of both hydrophilic and hydrophobic polymers, both types of drugs/growth factors can be entrapped inside the scaffold. The scaffold fiber was loaded with VEGF and bFGF as the matrix, and their bioactivity towards the human umbilical vein endothelial cells (HUVECs) was evaluated. The scaffolds showed the release of growth factors from the matrix activating the signal molecules for HUVECs. *In vivo* results showed the initiation of angiogenesis and mimicked the ECM. Microscopic results confirmed the structural changes in cell morphology, such as the formation of lamellipodia and filopodia. Similarly, for heart failure, cardiac progenitor cells (CPCs), which can differentiate themselves into various other cell types such as cardiomyocytes, endothelial cells, and smooth cells, were immobilized on the 3D culture conjugated with nanofiber scaffolds. Scaffold showed environment mimicking the ECM and improved the differentiation of iPSC-CPCs forming the cardiomyocytes and increased number of cardiac troponin R positive cells [111].

Congenital heart disease is by birth type of defect causing failure in the right ventricular of the heart. Researchers reported the preparation of cardiac patches containing child c-Kit+ progenitor cells in polycaprolactone nanofibers [112]. The presence of gelatin caused the increase in the metabolism of neonatal and child CPC. The extract collected from the patch showed a reduction of fibrotic gene expression in rat cardiac fibroblasts. Also, the extract showed a positive effect of tube formation of HUVECs, showing the angiogenesis nature of the patch. Similarly, Kang et al. reported immobilization of umbilical cord blood-derived mesenchymal stem cells seeding fibronectin on the polycaprolactone nanofibers and coating with poly (glycidyl methacrylate) [113]. The nanofibers stabilized cardiac function and inhibited left ventricle modeling in an animal model with MI. The scaffold promoted cell elongation and adhesion efficiency while angiogenesis and mesenchymal differentiation activities were also reported. The electrocardiogram (ECG) showed an increase in LV ejection fraction in the animal group treated. Also, the reduction in the size of MI and fibrosis was reported with an increase in scar thickness. PCL-based nanoscaffolds with thymosin $\beta 4$ coating functionalized with murine-derived cardiomyocytes to improve cardiac functions were also reported [114].

Silk is one of the older biopolymers and has been extensively used in various medical applications. Researchers exploited silk fibroin to prepare a PVA/silk fibroin-based nanofibrous heart patch using an electrospinning technique with the size of 228 nm [115]. The fiber was cross-linked via glutaraldehyde and prevented its degradation. Due to the presence of silk fibroin, the mechanical properties got enhanced with a minimal rate of degradation. The patch acted as excellent homing material for human cardiac fibroblast cells showing good cellular proliferation. Another group of researchers reported the trilayered patch consisting

Table 3: Nanofiber-based approaches for cardiovascular disease treatment.

Name of polymers used	Cells/drug entrapped	Diameter of fiber	Outcome of study	References
Molybdenum disulfide, reduced graphene oxide, and silk fibroin	TBX18-hiPSCs	450 nm	Scaffolds were able to induce cardiac differentiation and controlled self-renewal potency	[121]
Silk-fibroin, superparamagnetic iron oxide nanoparticles	Mouse embryonic cardiac cells	250 nm	The presence of silk fibroin supported cardiac differentiation; upregulation of cardiac genes such as GATA-4, cardiac troponin T, Nkx 2.5, and alpha-myosin heavy chain	[122]
Polyethylene terephthalate/graphene oxide	Human umbilical vein endothelial cells	147 ± 38 and 253 ± 67 nm	Improvement in cardiac electroconductivity, the substrate could support HUVECs; improved cardiac cell attachment and proliferation	[123]
Poly(l-lactic acid) and polyurethane	Rat cardiomyoblasts (H9C2 line), human and rat cardiomyocytes	178 ± 32 nm to 367 ± 66 nm	Prepared nanofibrous mats using solution blow spinning method; mats showed proliferation activity for reported cells	[123]
Peptide amphiphile	Fractalkine	n.m.	Targeted the fractalkine in carotid artery balloon injured model and showed 4.2-fold enhancement in fluorescence and increased dose-dependent manner	[124]
Poly(L-lactide-cocaprolactone)	Fibroblast-derived ECM	500 to 900 nm	Improvement in cell viability, molecular diffusion, and cell maturation	[124]
Polyvinyl alcohol, methylacrylate grafted lignin	Betulinic acid	~1 μm	Formulation proved to be noncytotoxic on normal endothelial cells, inhibited cytokine levels, increased vasodilators, and prevented myocardial cells from degeneration	[125]

of silk fibroin and PVA forming the middle layer as hydrophilic while the top and bottom layers were made from PCL and polylactic acid (PLA) using layer-by-layer technology. The patch showed biocompatibility against the human endothelial cells. SEM results confirmed the property of endothelial cells to get dispersed and get themselves adhere to the surface of patch forming endothelial cell layer [116].

Rufaihah et al. reported a nanofiber scaffold made of glycosaminoglycan mimetic peptide, capable of inducing angiogenesis after MI without any stem cells. Injecting nanofibrous gels increased VEGF-A expression and deployment of vascular cells for better cardiac performance [117]. Survival of cardiac performance could be accounted for by the overexpression of Ang-1 that activates the prosurvival pathway via interaction with integrin receptors of muscle cells and promotes survival [118]. Also, the presence of Ang-1 prevented the loss of cardiac myocytes. Overexpression of VEGF might be a reason for the activation and migration of the cardiac stem cell population for repairing MI [119].

Shojaie et al. prepared an on-demand drug release-based patch of gelatin and oligoaniline/PVA via electrospinning technique [120]. Owing to the hydrophobic nature of aniline oligomer, the increasing concentration decreased the diameter from 300 to 150 nm. Also, the increase in aniline oligomer increased conductivity, controlled thermal properties, and sustained drug released with a low degradation rate. The lower diameter of fibers exposed a high surface area to surroundings, and degradation is enhanced. However, due to the presence of oligoaniline, the penetration of media is restricted and repels the aqueous media, thus lowering the degradation rate. Work done by other researchers has been cited in Table 3.

Polyvinyl alcohol (PVA)/chitosan nanofibers electrospun using MWCNT-incorporated polyvinyl alcohol (PVA) were made by Liao et al. Microwave carbon nanotubes (MWCNTs) were introduced into PVA and chitosan fiber blends (160 nm diameter) [126]. MWCNTs (7-15 nm in diameter) were attached to hydrophobic polycaprolactone (PCL) sheets and nanofiber meshes by Wickham and colleagues using thiophene. Mechanical strength might be increased without altering mesh shape in this group. Increased cardiac progenitor cell (CPC) proliferation was also seen when thiophene-conjugated CNTs were added to PCL polymers [127].

The alignment, mechanical toughness, and electrical conductivity of fibers were significantly improved when CNTs were incorporated into other materials, including gelatin nanofibers and poly (glycerol sebacate) (PGS). The cardiomyocytes were able to beat strongly and synchronized because to the improved substance. An increase in Cx43 expression and a decrease in the excitation threshold were achieved by adding CNTs. Aside from that, CNTs enhance the scaffold's ability to imitate the left ventricle's anisotropic structure [128]. PLGA and CNF composites were studied by Stout et al. for cardiomyocyte function. They found that CNFs improved the conductivity and cytocompatibility of PLGA, which in turn boosted the adhesion and proliferation of cardiomyocytes. CNFs also boosted the density of cardiomyocytes (up to 25 : 75 wt percent PLGA:CNFs). The addition of CNFs of any diameter improved the electrical conductivity of PLGA/CNF composites [129]. A new injectable scaffold for cardiac tissue engineering was developed by Meng et al. [130] by combining CNFs, self-assembling rosette nanotubes (RNTs), and poly (2-hydroxyethyl

methacrylate) (pHEMA) hydrogel. The density of cardiomyocytes in the pHEMA hydrogel rose when more CNFs and RNTs were introduced into the matrix. CNFs enhanced conductivity and surface roughness but decreased tensile modulus and contact angle when added to composites. Patterns of aligned CNFs (100 nm in diameter) were produced on the surface of PLGA by Asiri et al. to replicate the anisotropy of the myocardium (50 : 50 PGA:PLA weight ratio). According to the findings, CNF alignment enhanced the scaffold's cardiomyocyte density. Comparing a vertical (0.1 S/m) and horizontal (0.0025 S/m) conductivity of the PLGA scaffold with that of genuine heart tissue revealed that aligning the CNFs improved both the vertical and horizontal (0.0025 S/m) conductivities.

To imitate the ECM, various synthetic biomaterials were designed with a nanoscale level of detail. Cardiac tissue may be formed by using the 3D growth and differentiation of cardiomyocytes in the NF poly (L-lactic acid) matrix [131]. Structures with varied PCL/PGA proportions in the PCL and poly glycolic acid NF scaffolds maintained live cells that expressed the major cell marker proteins of cardiomyocytes, smooth muscle cells, and endothelial cells (ECs) inside the subcutaneous tissue of mice [132]. It is generally accepted that synthetic or biological polymeric biomaterials, like cardiac patches, may aid cell organization but, owing to their inherent weak conductivity, restrict the patch's capacity to contract, in general. In order to do this, a polymeric patch must be strengthened or implanted with conductive nanoparticles utilizing several ways [133]. Cardiac tissue engineering scaffolds and patches may be made from electroactive materials, including polypyrrole, polyaniline, and polythiophene, which have been shown to be effective. Biocompatibility and biodegradability are two of the most pressing issues that need to be addressed, but the ability of biomaterials to be changed is also a concern. Since electrically conductive nanostructured materials may be used in cardiac tissue engineering, additional research is needed to understand their potential usage [134]. Polymeric nanoparticles may be used to change cardiac patches, but their usefulness as drug delivery methods to treat myocardial infarction must not be overlooked. NPs made from deblock copolymers of poly (ethylene glycol) and poly (propylene sulphide) (PPS), loaded with ginsenoside Rg3, have been shown in a rat ischemia-reperfusion model to enhance heart function and decrease infarct size by decreasing oxidative stress, inflammation, and fibrosis [135].

Myocardial ischemia-reperfusion may be treated effectively and efficiently by infusing appropriate dosages of anti-inflammatory medication (adenosine) into multilayered scaffolds with cardio-inductive effects on stem cells [136]. There is an improved therapy for reperfusion damage using polymeric core shell polymeric nucleic acids with adenosine-core shell polymeric NPs [137]. To improve cardiac scaffolds after an AMI, polymeric nanoparticles capable of recognizing particular ECM metalloproteinase have also been tested [138].

3.4. Carbon Nanomaterials. Carbon being the eternal element has shown its good nature in the medical field also. Carbon not only forms strong bonds but is also nontoxic to normal cells. Due to its nanoscaling, high thermal conductivity, and high affinity towards interaction with proteins, carbon nanomaterials (CNMs) prepare a 3D environment for the growth of cardiac cells [125]. CNMs have also been reported as proliferation, differentiation, and maturation medium for various cardiac cells [139–142].

Based on novel properties of CNMs, Tashakori et al. prepared CNM-based collagen scaffold for repairing the myocardial-based injury [143]. The collagen-CNM scaffolds impregnated into damaged heart tissue were able to improve the repair of the heart, and no toxic response was visible. The material also induced neovascularization. Stout et al. [129] prepared PLGA and carbon nanofiber-based material for cardiac application. The presence of CNM caused the increase in conductivity, and cytocompatibility in a dose-dependent manner also promoted the adhesion and proliferation of cardiomyocytes.

Ataei et al. [144] used CNMs in the preparation of heart valves. The researchers functionalized a carbon nanotube with heparin and combined heparin functionalized carbon nanotube (HCNT) with plasma-treated polyurethane using the solvent casting method. The presence of heparin resulted in surpassing the dispersal and calcification resistance for CNMs. Also, the addition of CNT to the matrix caused enhancement in modulus. The initial results with L929 cells showed no cytotoxicity and were more blood compatible. The contact angle increased remarkably with the introduction of OVS. Also, the adhesion increased towards the L929 fibroblast cells. Similar results were reported for the platelet adhesion test. Pyrolytic carbon is a common material used for biomedical engineering but is prone to microbial attack. Silver nanoparticle (Ag-NP) deposition used the pulsed laser deposition technique. Ag-NPs have proven activity against gram-positive and gram-negative bacteria; thus, the microbial load can be reduced [145].

Ahadian et al. [146] reported the use of CNMs for cardiac tissue engineering. Researchers combined CNTs with poly (octamethylene maleate (anhydride) 1,2,4-butanetricarboxylate) using UV light as a crosslinker for preparing elastomeric scaffold. With the increase in CNT content, surface moduli of scaffold increased while bulk moduli decreased. The decrease in CNT content resulted in a significant reduction in tissue maturity. The scaffolds also showed coordinated beating with the cardiomyocyte cells. Chitosan is one of the most reported biopolymers for biomedical applications. Chitosan has been coupled with carbon nanomaterial for cardiac tissue engineering. Martins et al. reported the formation of composite scaffolds with carbon nanofibers dispersed in chitosan solution. The scaffolds showed a seeding nature for neonatal rat heart cells; after 2 weeks, the pores of scaffolds were filled with cells. The presence of carbon nanofibers caused enhancement in the expression of cardiac-specific genes required for contraction and electrical coupling [147].

Hybrid hydrogels of reduced graphene oxide and gelatin methacryloyl were reported for cardiac tissue engineering [148]. The hydrogel thus formed has enhanced electrical conductivity and mechanical properties. The hydrogel

Table 4: Tabulated literature citing carbon nanomaterials for cardiovascular diseases, where n.m. is not mentioned.

Type of carbon nanomaterial	Name of polymer	*In vivo* studies	Electrical interpretation	Size	Biological interpretation	References
Carbon quantum dots (CQD)	Poly glycerol sebacate; polycaprolactone	n.m.	The presence of QD, increased electrical conductivity	376.82 ± 150 nm	1% CQD, decreased cell viability; 0.5%CQD, persisted cell viability	[149]
Carbon nanotubes (CNT)	Polyurethane, chitosan	H9C2 cells	Increase in electrical conductivity	n.m.	Biocompatible with H9C2 cells	[150]
p-Phenylenediamine surface-functionalized CQD	Silk fibroin/ polylactic acid	Rat cardiomyocytes	Improved electrical conductivity among cardiomyocytes	n.m.	Increased cardiac marker gene expression	[151]
Carbon nanotubes (CNT)	Polyvinyl alcohol, chitosan	Rat mesenchymal stem cells	The presence of large quantities of CNT, decreased electrical conductivity	255 ± 3.5 to 307 ± 5.9 nm	Expression of Nkx2.5, Troponin I, and β–MHC cardiac marker increased significantly	[152]
Carbon nanotubes (CNT)	Gelatin with methacrylate anhydride	Neonatal rat ventricular myocytes	Showed apparent spontaneous electrical conductivity; Beta1-integrin pathway was involved in modulation of electrical impulses	n.m.	Increase in expression of p-FAK and RhoA in cardiac constructs	[153]
SWCNTs	Gelatin	Rat H9c2 cells	n.m.	n.m.	Increased expression, proliferation, and differentiation	[154]
MWCNTs functionalized with carbodihydrazide	n.m.	HL-1 cardiomyocytes	The electrical conductivity of the scaffold was 0.015 S/cm	166 nm	Improved heartbeat and cellular viability	[155]
MWCNTs	PCL	Rat H9c2 cells	Conductivity increased with PCL content	n.m.	Myoblast cells showed adherence for 4 days	[156]

supported cellular differentiation and proliferation of NIH-3T3 cells. Also, the cardiomyocytes showed contractility and a faster heartbeat. The scaffold has a mechanism for electrical current flow, thus reducing charge distribution and potential propagation impedance. Work done by other researchers has been cited in Table 4.

Research by Kaya et al. used an electroconductive hydrogel created by reinforcing reduced graphene oxide (rGO) into an acid-gelatin-poly (ethylene oxide) (PEO) hydrogel in order to evaluate the kinetics of irbesartan's drug release. Angiotensin receptor blockers (ARBs) are used to treat excessive blood pressure in individuals with CVD. Irbesartan belongs to this family. Models of irbesartan kinetics from electroconductive hydrogel are used in this work to mimic and analyze release kinetics. According to the study, the hydrogel that contained 20% rGO successfully released irbesartan over the course of 10 days. As a medication carrier for treating CVDs, this composite demonstrates the effectiveness of rGO in hydrogel [157]. The release kinetics of diltiazem were studied in a work by Sarkar et al. using a drug carrier membrane made from GO and methylcellulose (MC). Diltiazem, a calcium channel blocker, is used to treat arrhythmias and high blood pressure. To ensure effective and regulated drug release, the researchers in this work used a GO/MC composite matrix [158].

CNTs functionalized with PEI/polyamidoamine dendrimer (PAMAM) were used to deliver miR-503 oligonucleotides to increase angiogenesis during CVD in another investigation. CNTs have been shown to be effective in delivering miR-503 and promoting angiogenesis [159]. The use of CNTs in stent coating has also been shown to inhibit in-stent restenosis by delivering angiogenic chemicals. Endothelial dysfunction and enhanced smooth muscle cell proliferation surrounding the stent may develop after stent implantation in the coronary artery. There is an increased risk of heart attacks and other symptoms as a consequence of this fast reocclusion of the coronary artery, which may be connected with recurring heart attacks. Polyacrylic acid (PAA) coated SWCNT in a fibrin hydrogel containing angiopoietin-1 and VEGF was designed by Paul et al. to address this issue. A canine model was used to evaluate the effectiveness of this mixture. Biohybrid stents like this one increased reendothelialization, reduced necrosis development, and avoided stenosis in the wounded arterial segment [160]. It has been shown that MWCNTs, GO, and carbon black can be used as drug transporters in research by

Renyun et al. According to this research, GO had the largest loading capacity among the CNMs studied (i.e., there are additional parameters, such pH and functionalization, that have a role in the release profile of medication, according to this research) [161].

Graphene's toxicity in biological systems is mediated by its planar dimensions, particle concentration, and surface characteristics [162, 163]. Long-term graphene exposure and buildup in cells produces inflammation, lasting genetic damage, and cell death [164]. The size and dispersion of graphene nanosheets are key challenges that must be addressed in order to reduce toxicity in a biological system. GO and hydrophobic graphene generated oxidative stress in the lungs, while hydrophobic graphene dispersed in pluronic was biocompatible and evoked no toxicity in vivo, according to Duch et al. This work emphasised the significance of surface functionalization and dispersion in improving graphene biocompatibility [165]. Chen et al. used different diameters of GO (50–200 nm, 500 nm, and >500 nm) at varied doses (0.1, 1, 10, and 100 mg/L) to evaluate their impact on embryonic zebrafish development. According to this study, GO at 100 mg/L concentration resulted in a longer hatching time for zebrafish embryos, shorter body length, changes in heart rate and blood flow, and an increase in apoptotic gene expression. When the concentration of GO exceeded 10 mg/L, the toxicity was not dependent on the size of the GO [166]. As a result, selecting the size and dosage of CNMs is critical for their safety and effectiveness in therapeutic applications.

Conjugating harmless chemical groups or eliminating reactive functional groups on the surface of graphene-based composites is commonly used to make them biocompatible. The toxicity of SWCNTs and acid functionalized SWCNTs was assessed in mice using oropharyngeal aspiration in one research. Acid functionalized SWCNTs were found to promote neutrophil and edoema production in the lungs in a dose-dependent manner [167]. Because of its bulky and massive size, CNTs tend to cluster in aqueous solutions compared to smaller CNMs that can be readily dispersed. This is the primary cause of CNM-mediated cell toxicity [168].

3.5. Dendrimers. An adequate description of dendrimers' structure may be found in the Greek word for "tree," dendron, which translates to "branch" [169]. With their multibranched, three-dimensional structure, and low polydispersity, dendrimers are really unusual [170]. Dendrimers, as nonviral vectors for therapeutic applications, seem to have numerous benefits over other nanotechnologies. They are superior to other viral and nonviral equivalents because of their high solubility, higher stability, low immunogenicity, and capacity to support the successful transport of therapeutic molecules, DNA, and RNAs [171]. Due to the nanoscale environment provided by considerable branching, the focal core of a dendrimer has been used to host chemical species. The perimeter of dendrimers may show a variety of functional groups, enabling them to interact with the surrounding molecular environment and with other dendrimers. Additionally, the dendrimer's repeating units enable the modification and encapsulation of pharmacological molecules inside the dendrimer [172].

To prevent atherosclerosis, it has these properties; thus, it may be crucial [173]. For injured tissue, NO encapsulation inside dendrimers has been found to be an effective treatment option. Poly (propylene imine) dendrimers have been shown to successfully release NO, suggesting that they might be used as drug delivery systems in the future [174]. Attempts have been made to regulate the elevation of inflammation at specific areas inside injured vasculature using dendrimers with promise as gene delivery vehicles for treating CVDs. Dendrimers containing DNA plasmids have been demonstrated to boost the gene's survival, stability, and vitality in the nucleus indicating that they might be used as potential therapeutic agents [175].

Overstimulating, the heart and blood vessels may lead to fibrosis and vascular and cardiac hypotrophy. Overexpression of angiotensin II, a peptide implicated in the RAAS, may lead to heart disease and cardiac remodeling. Cardiovascular disease may be prevented and treated by the reduction of its activation. The angiotensin II receptor type 1 is responsible for the majority of angiotensin II's harmful effects (AT1R). To lower AT1R expression in an ischemia-reperfusion paradigm, PAMAM dendrimers were utilized as siRNA carriers [176]. Nifedipine has a limited bioavailability in the human body because of its low water solubility throughout a pH range of 4–13. A pH of 7 improved the water solubility of nifedipine in amine or ester-functionalized PAMAM dendrimers G0 to G3. It was found that the ester functional groups were more effective than the amine ones on the surface. PAMAM dendrimers may solubilize nifedipine in order to enhance its therapeutic properties [176].

To combat CVD, researchers have turned to gene therapy, and as a result, several have investigated ways to better deliver genetic material to the desired locations, as well as ways to control the upregulation of inflammatory genes using nanocarriers such as cationic liposomes. Cationic liposomes, like dendrimers, bind polyanionic DNA and deliver it to cells. Gene transfer into mouse cardiac grafts was studied using a G5 dendrimer with an ethylenediamine core. X-Gal labeling revealed a 1000-fold increase in G5 dendrimer expression in both myocytes and graft filtering cells over the course of seven to 28 days. Dendrimers were found to improve plasmid survival rates [177–180].

In the nucleus, dendrimer improved gene stability and viability. Higher transfection and viability may be achieved by lowering the charge ratio of DNA to dendrimer [181]. The same was done by Turunen et al., who compared the transfection efficiency of different lipids and fractured PAMAM and poly ethylenimine (PEI) dendrimer in vitro against smooth muscle cells (SMC) as well as endothelial cells (ECV 304) and chose fractured G6 PAMAM dendrimer and PEI dendrimer with 25 kDa and 800 kDa for in vivo studies. They stated that transfection was dependent on charge ratio and observed that the highest transfection efficiency was shown by fractured dendrimer at charge ratio 6, and as the charge ratio increased, cell survival rate decreased for fractured dendrimer as well as PEI dendrimer, but the

survival rate was higher in fractured dendrimer between both dendrimers. In vivo experiments indicated that β-galactosidase activity with a broken dendrimer at a charge ratio of 3 was the most effective transfection method. It was shown that the transfection effectiveness of PEI and fragmented dendrimer was greater than that of liposomes and cationic-plasmid liposomes [182]. Gene transfer and expression in the mouse vascularized transplant model may be improved using the G5 EDA core dendrimer. β-Galactose expression was monitored for 7 to 14 days after the plasmid pMP6A β-gal expressing β-galactose was combined with dendrimer and perfused into coronary arteries. They also found a charge ratio of 1 : 20, and serotonin incubation for two hours increased the expression [183]. The electroporation and DNA/dendrimer combination improved gene transfer in a mouse heart transplant study by Wang et al. Electroporation of β-galactosidase reporter gene and starbust PAMAM dendrimer into live human myocardium resulted in a 10- to 45-fold increase in gene expression [184]. By connecting mAb to PAMAM dendrimer in tissue that expresses overexpressed adhesion molecule P- and E-selectin on activated endothelial cells, it is possible to increase the effectiveness of transfection. They employed avidin and biotin to cross-link anti-E/P selectin antibody to a premade superfect DNA complex, which was then used to transfect a reporter gene into the E-selectin-expressing cells of CHO cells [185].

One disadvantage of dendrimers is that they frequently have highly charged exteriors due to their high number of branches at their surface, each with their own surface charge; this can often result in either a highly cationic or highly anionic nature, which can lead to toxicity issues if not fully addressed [186].

3.6. Cell Membrane Coated Particles. As an alternative to PEGylation, cell membrane coating technology relies on natural cell membranes to protect manufactured NPs. Coating NPs with functional membrane proteins on their surface helps them escape the body's immune system and prolong their circulation (better biocompatibility), but it also provides them with numerous cell-like biofunctions because of their ability to mimic cell membrane proteins (cell-mimicking properties). Hu et al. were the first to cover PLGA nanoparticles with an erythrocyte membrane [187]. Their work employed hypotonic medium hemolysis to remove the RBC membrane, which was then fused with PLGA NPs to produce RBC membrane camouflaged NPs (RBC-NPs). In addition, they demonstrated that the RBC membrane proteins were transferred onto PLGA NPs effectively. As a further bonus, the RBC membrane-coated NPs remained stable even after six hours of coculture with HeLa cells. Consequently, a nanoplatform has an exceptional potential to evade immune clearance, allowing it to remain in the body for an extended period of time. This nanostructure might be used as a generally effective medication delivery platform against CVD if small-molecule medicines are placed into the inner PLGA core. PLGA NPs encased in RBC membranes (RBC/RAP@PLGA) have been described by Wang et al. After treatment with this nanoplatform, the average area ratio of plaque to vascular lumen dropped from 47.95 percent to 31.34 percent, which was superior to the free medication group in terms of advancement of atherosclerosis (from 47.95 percent to 42.42 percent) [188].

Platelet membrane-coated PLGA NPs produced by Hu et al. were the first to show preferential attachment to injured human and rodent vascular tissue and MRSA252 [189]. With the right loading agents, these platelet membrane-coated nanoformulations might be used to treat thrombosis, arterial damage, and sepsis. Platelet membrane-coated PLGA nanoparticles (PNPs/LBK) were manufactured by Wang et al. in order to combat the formation of thrombus [190]. Consequently, PNP/LBK has a greater potential to target thrombuses while reducing the danger of hemorrhagic complications.

In the event of a thrombus, a hypoxic environment increases the formation of ROS and tissue destruction in the affected area. Platelet membrane-encased argatroban-loaded polymeric nanoparticles (PNPArg) were recently produced by Zhao et al. to treat thrombus. An anticoagulant medication known as argatroban has been shown to have excellent therapeutic benefits on many thrombotic illnesses, and the inner core of their method is poly (vanillyl alcohol-cooxalate) (PVAX), an H2O2 degradable polymer that is capable of scavenging excess ROS [191].

Virus-like particles (VLPs) are naturally occurring viral genome encapsulators. To a growing degree, theranostic platforms using VLPs are becoming more popular due to their many advantages over traditional theranostic platforms. Examples of VLP cargo molecules include chemotherapeutic medicines, small interfering RNAs (siRNAs), RNA aptamers, proteins, and other peptides and proteins, among others [192–194]. A targeting function may be added to VLPs by genetic engineering. Insertions or extensions of peptides and proteins may be directly inserted into the main amino acid sequences of the coat proteins (CPs), allowing their presentation on either the interior or outer surface of the VLP [195–197].

Trifunctional SV40-based NPs were produced by Sun and colleagues to transport Hirulog peptide. Near-infrared quantum dots (CGNKRTRGC) and cyclic peptides (CGNKRTRGC) were put into the nanosystem for targeting the p32 protein on macrophages. NPs that were specifically targeted by ApoE(-/-) mice produced a fluorescent signal in the plaques that was three times brighter than that of untargeted particles. In ApoE knockout mice, SV40 NPs delivered Hirulog to atherosclerotic plaques. Mice injected with SV40 NPs had more antithrombin activity in their aortae than those injected with SV40 NPs that were not treated. Atherosclerosis medication delivery and molecular targeting will both benefit from this novel kind of NP [198].

4. Challenges for Nanomedicines for CVD

It is impossible to tell how long a nanomaterial has been present in a biological cell. There is insufficient long-term evidence to provide an accurate approximation of a definitive response. The possible negative consequences of a foreign body inside a live cell are also up in the air at this

point. The negative impacts of nanomedicines at the cellular level may express themselves as symptoms at the level of the patient's body. However, there is no consistent evidence available on the biological safety of NPs at the current time. Although safety guidelines and tests have been created, hazard and risk identification is now done on a case-by-case basis, rather than in bulk. The chemical composition of the nanoparticle has the potential to produce direct toxicity inside a live cell. The chemical structure of the particles determines the toxicity of nanoparticles. For example, the toxicity of carbon nanotubes is a direct result of the mechanical structure, size, kind of carbon isotope employed, surface coating, and relative carbon concentrations of the nanotubes in question.

The protein corona formation is a major issue in focused nanomedicine. Once in the bloodstream, the nanocarriers are opsonized, meaning they are phagocytized by MPS and subsequently expelled. The protein in question has been widely investigated for a decade and is called protein corona [199]. In interaction with biological fluids, proteins create protein coronas on NPs. The protein corona may influence the biological destiny of nanocarriers by enhancing mononuclear phagocyte system absorption [200, 201]. Protein corona has been found to be deleterious to active targeting techniques as well as MPS absorption [202]. The biological corona coating reduces the selectivity of the targeted ligand [203]. For example, following incubation with plasma, transferrin-modified silica NPs lost their targeting capacity [204]. Despite considerable attempts, few viable solutions have been developed to reduce corona-induced mistargeting. One method involves coating NPs with zwitterionic chemicals. For example, zwitterionic coatings have produced corona-free Au-NPs [205].

Recent research has demonstrated that iron compounds may cause ferroptosis, a novel kind of programmed cell death linked to I/R damage [206]. The Fenton reaction/iron metabolism leads to excessive ROS generation, resulting in regulatory cell death [207]. These results question the usage of iron-based NPs and advice professionals to choose NP composition carefully. Long-term usage of nondegradable inorganic NPs requires evaluation of their biological destiny and safety. The liver proteolytic enzymes may destroy polymeric-coated Au-NPs. This shows that the NP physicochemical qualities may change in vivo, causing unwanted toxicity, aggregation, or immunological activation. The altered physical and chemical features of NPs complicate the inflammatory response of the human immune system, causing greater unfavorable consequences on the heart failure process. Thus, additional research on NP biological destiny is required [208].

The nanobiointeraction is one of the primary hurdles in translating theranostic nanomedicine to clinics. When nanomedicine interacts with biological material, it may cause immune reactions, inflammation, or other illnesses. The hazardous impact of nanoformulations is highly dependent on size, zeta-potential, and solubility [209]. When nanoparticles enter a biological system, they interact with proteins, forming a surface "corona." It also changes their size, stability, dispersibility, pharmacokinetics, biodistribution, and toxicity [210]. Also, several nanoplatforms elicit an immediate adverse immunological response called complement activation-related pseudo allergy [211, 212]. Thus, studying nanomedicines' physicochemical properties in relation to pathophysiology and disease heterogeneity is vital. Furthermore, theranostic nanomedicine is not a one-size-fits-all notion, since therapy differs from person to person [213]. Theranostic nanomedicines are also challenging to synthesize in a controlled and repeatable manner. Large-scale nanoparticle production has poor batch-to-batch repeatability, variable physical and chemical properties, and low yield. Due to the difficulty imposed to pharmaceutical firms, nanoplatforms with arduous and sophisticated production procedures seldom make it into the clinic [213, 214]. Since theranostic nanoparticles are multifunctional units, more accurate chemistry, manufacture, and control are required, coupled with excellent manufacturing practice.

A third key problem is the large gulf between scientists and regulatory bodies. Many government rules regulate the commercialization of nanomedicine based on quality control, manufacturing methods, safety profile, and patent protection. The lack of clear regulatory and safety requirements hinders timely and successful theranostics market translation [215].

Determining the relationship between patient biology and disease heterogeneity and nanomedicine can help overcome the biological limitations of nanotheranostics. Before starting clinical trials, nanoformulations must be thoroughly tested in several preclinical animal model systems. For treating and imaging human patient groups, preclinical investigations in animal models are often beneficial [216]. The early phases of clinical development need the use of nanotoxicology profiles consisting of standardised laboratory procedures for assessing patient risk [211, 217]. Noncancer disorders have normal vascular architecture; thus, developing nanotheranostics for them is important. Making biomimetic NPs that mimic natural cell functions (such as secretory chemicals, cell surface markers, and extracellular matrix) has a lot of promise for theranostic use. Using stimuli-based smart nanoparticles to deliver therapeutic loads selectively at the site of action may enhance theranostics' real-world effectiveness. Personalized treatment plans for illnesses with heterogeneity, malignancy, and adaptability may benefit from real-time monitoring and provision of this kind. Academia is the source of nanoparticle-based medicinal delivery methods. They often understand the technological problems encountered by industry in commercializing techniques. To close this gap, increased coordination between labs and drug firms is needed. GMP modifications for large-scale theranostic NP production are required.

5. Future Perspective

The status of nanomaterials is midway. Though nanomaterials had been exploited to some extent, some groundbreaking research is still on its way. The use of three-dimensional printing is not new in the pharmaceutical world. It has been used in various applications, such as dosage form

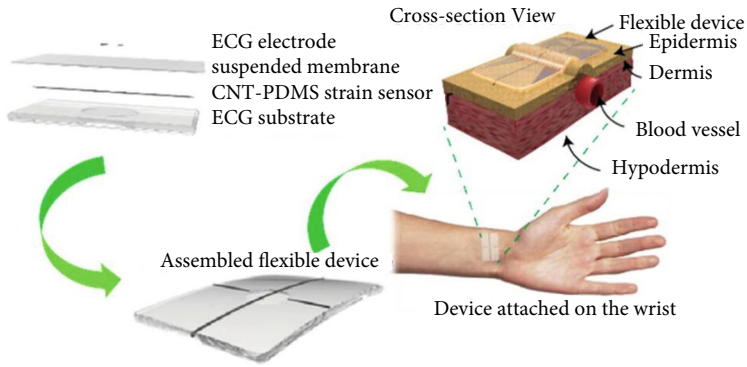

Figure 2: Schematic of the CNT-PDMS wearable device structure for measurement of wrist pulse pressure and ECG. Here, the ECG signal was captured by the flexible CNTPDMS ECG electrodes. The shape change of blood vessels during a wrist pulse induced the resistance change of the CNT-PDMS strain sensor. Reproduced with permission from reference [222].

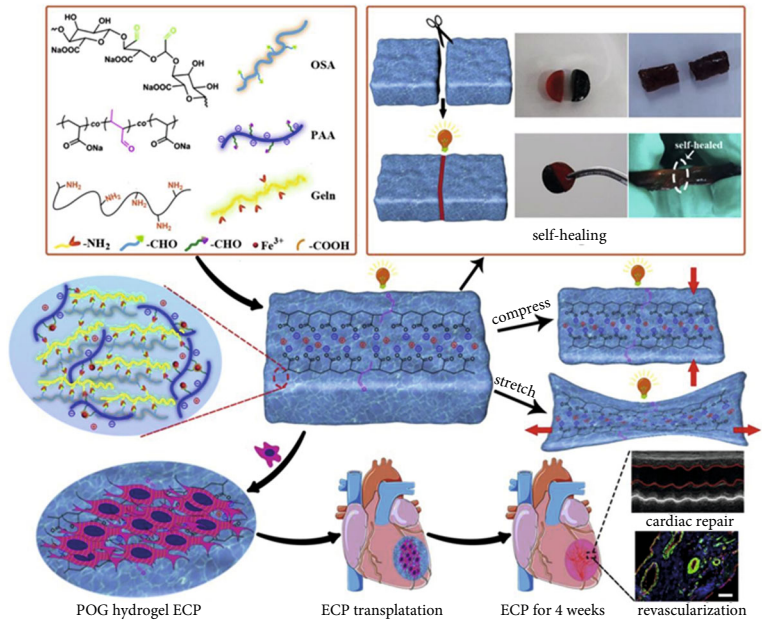

Figure 3: Schematic illustration about the tunable self-healing POG1 hydrogel fabrication and its application in myocardial infarction repair. Reproduced with permission from reference [223].

preparation to complex tissue recreation. It consisted of bioink (material containing active or cells), printer, and substrate [218]. Ho et al. reported the fabrication of cardiac tissue scaffolds using PCL and CNTs supported the proliferation of H9C2 cells [156]. Kanawati et al. reported the fabrication of a heartbeat synchronization device for a 76-year-old patient with congenitally corrected transposition of the great arteries (ccTGA) [219]. A precise 3D model with anatomic specification, same as that of the patient body, was printed. 3D printed heart models can also help understand the patient's status better and help find the solution for surgery procedures [220].

Apart from 3D printing, now sensors are also conjugated as point-of-care devices. Rezaei et al. reported the fabrication of sandwich-type immunosensor-based carboxylated multiwalled carbon nanotube for detecting the cardiac Troponin I. These nanofibers were fabricated in carbon electrode and utilizer enzyme-labeled amperometric immunoassay and immobilized horseradish peroxidase enzyme. The detection limit ranged from 0.5 to 2 ng mL^{-1} in the case of the average person, while in the case of an infarcted patient, > 20 ng mL^{-1} was the limit [221].

Su et al. reported a wearable device measuring CNT and polydimethylsiloxane's electrical impulses based on piezoresistance and voltage sensing phenomenon [222]. The device measured wrist pulse pressure and cardiac electrical signal based on the change in resistance and pressure with device sensitivity of 0.01 Pa-1. The device can be worn on the wrist, and ECG signals after physical activity are transmitted using Bluetooth, and data is captured on a mobile phone and analyzed as an early warning (Figure 2). Due to regular movement of the heart and associated parts,

extensive wear and tear are observed; these polymer patches and scaffolds have lower life. To solve this problem, Song et al. prepared self-healing ionic hydrogel made of polyacrylic acid and oxidized alginate (OA)/gelatin (POG) (as shown in Figure 3) [223]. The hydrogel showed super stretchability (>500% strain) and compressive strength (>85% strain). The hydrogel showed more oriented sarcomeres than the control group after *in vivo* results showed robust left ventricular remodeling and restoring heart functionality.

Initially, percutaneous coronary lumen enlargement was treated with balloon angioplasty, also known as plain old balloon angioplasty. Though this technique persisted in the market for many decades, the risk of abrupt closure and nondurability and restenosis decreased its trend [224–226]. Later, the metallic stents took their place and shown remarkable results in improving procedural success, but they were costly [227–229]. However, they were considered as standards in their use and rule market for many years. Plastic stents and metallic stents had similar output; no significant difference was observed [230]. Later, drug-eluting stents come into play. A clinical trial comparing metal stents and drug-eluting stents on patients with antiplatelet therapy showed drug-eluting stents better with low mortality, MI, and stroke [231]. In a clinical trial conducted on biodegradable drug-eluting stent containing sirolimus and everolimus, a total of 1300 patients participated [232]. The stent with sirolimus elution showed better results due to lower lesions of the ischemic heart observed. Three-dimensional printing can also be hyphenated with the stent preparation [233]. Thus, there is still a way ahead in terms of clinical trials and its usefulness in regular day life.

6. Conclusions

As theranostic agents, nanotechnology and nanomedicine may be utilized to detect and treat cardiovascular problems. To distribute drugs to injured regions, small particles act as nanodevices or nanotransporters. Nanocarriers offer promise for effective, tailored medicine, and gene delivery that overcomes challenges of solubility, bioavailability, and other pharmacokinetic aspects. Many CVDs, treatment choices, and current medical breakthroughs are discussed in this paper. It highlights the progress made in the administration of drugs to cardiovascular tissues with greater precision. Studies in the lab and in the animal model of several cardiovascular nanoformulations have yet to be translated into the clinic. It handles pharmaceutical scale-up, release efficiency, important regulatory constraints, and Good Manufacturing Practice (GMP). *In vivo* and clinical studies are required to determine the full effect of nanoparticles on the human body and cardiac tissues. Future CVD nanocarrier designs and advancements will require additional investigation. Cardioprotective characteristics of a number of natural substances are awaiting further research and clinical translation. Several challenges hinder the practical application of nanomedicine in CVDs. Institutional and industrial interests, lack of sufficient infrastructure and skills to prepare patients for treatment, efficient monitoring of patient outcomes, registration of patients in clinical trials, and country-specific remuneration and cost are among the difficulties. Thus, nanoparticle translational medicine in CVDs should encompass bioengineers, pharmacists, chemists, biologists, and clinicians. Future investigation will leverage peptides and antibodies to detect CVD markers and build personalized nanodelivery systems. Future nanocardio medicine will research novel nanosystem clinical implications to promote quality of life.

Conflicts of Interest

We wish to confirm that there are no known conflicts of interest associated with this publication, and there has been no significant financial support for this work that could have influenced its outcome.

Authors' Contributions

Hitesh Chopra, Shabana Bibi, and Awdhesh Kumar Mishra contributed equally to this work.

Acknowledgments

The authors gratefully acknowledge the Deanship of Scientific Research, King Khalid University (KKU), Abha-61421, Asir, Kingdom of Saudi Arabia, for funding this research work under the grant number R.G.P1./291/43.

References

[1] S. S. Virani, A. Alonso, H. J. Aparicio et al., "Heart Disease and Stroke Statistics-2021 Update A Report from the American Heart Association," *Circulation*, vol. 143, no. 8, pp. E254–E743, 2021.

[2] R. S. Paffenbarger, R. Hyde, A. L. Wing, and C. Hsieh, "Physical activity, all-cause mortality, and longevity of college alumni," *The New England Journal of Medicine*, vol. 314, no. 10, pp. 605–613, 1986.

[3] J. Stevens, J. Cai, K. R. Evenson, and R. Thomas, "Fitness and fatness as predictors of mortality from all causes and from cardiovascular disease in men and women in the Lipid Research Clinics Study," *American Journal of Epidemiology*, vol. 156, no. 9, pp. 832–841, 2002.

[4] F. B. Hu, W. C. Willett, T. Li, M. J. Stampfer, G. A. Colditz, and J. E. Manson, "Adiposity as compared with physical activity in predicting mortality among women," *The New England Journal of Medicine*, vol. 351, no. 26, pp. 2694–2703, 2004.

[5] J. W. Rhee and J. C. Wu, "Advances in nanotechnology for the management of coronary artery disease," *Trends in Cardiovascular Medicine*, vol. 23, no. 2, pp. 39–45, 2013.

[6] W. Jiang and H. Liu, "Nanocomposites for bone repair and osteointegration with soft tissues," in *Nanocomposites for Musculoskeletal Tissue Regeneration*, Woodhead Publishing, 2016.

[7] H. Liu and T. J. Webster, "Nanomedicine for implants: a review of studies and necessary experimental tools," *Biomaterials*, vol. 28, no. 2, pp. 354–369, 2007.

[8] O. Pagliarosi, V. Picchio, I. Chimenti, E. Messina, and R. Gaetani, "Building an artificial cardiac microenvironment:

a focus on the extracellular matrix," *Frontiers in Cell and Development Biology*, vol. 8, p. 8, 2020.

[9] R. Ravichandran, V. Seitz, J. Reddy Venugopal et al., "Mimicking native extracellular matrix with phytic acid-crosslinked protein nanofibers for cardiac tissue engineering," *Macromolecular Bioscience*, vol. 13, no. 3, pp. 366–375, 2013.

[10] C. M. Kelleher and J. P. Vacanti, "Engineering extracellular matrix through nanotechnology," *Journal of the Royal Society Interface*, vol. 7, suppl_6, pp. S717–S729, 2010.

[11] J. Hrkach, D. Von Hoff, M. M. Ali et al., "Preclinical development and clinical translation of a PSMA-targeted docetaxel nanoparticle with a differentiated pharmacological profile," *Science Translational Medicine*, vol. 4, no. 128, p. 128ra39, 2012.

[12] H. S. Choi, W. Liu, F. Liu et al., "Design considerations for tumour-targeted nanoparticles," *Nature Nanotechnology*, vol. 5, no. 1, pp. 42–47, 2010.

[13] Y. Liu, E. D. Pressly, D. R. Abendschein et al., "Targeting angiogenesis using a C-type atrial natriuretic factor-conjugated nanoprobe and PET," *Journal of Nuclear Medicine*, vol. 52, no. 12, pp. 1956–1963, 2011.

[14] M. D. Majmudar, J. Yoo, E. J. Keliher et al., "Polymeric nanoparticle PET/MR imaging allows macrophage detection in atherosclerotic plaques," *Circulation Research*, vol. 112, no. 5, pp. 755–761, 2013.

[15] H. P. Luehmann, E. D. Pressly, L. Detering et al., "Pet/ct imaging of chemokine receptor CCR5 in vascular injury model using targeted nanoparticle," *Journal of Nuclear Medicine*, vol. 55, 2014.

[16] H. Soo Choi, W. Liu, P. Misra et al., "Renal clearance of quantum dots," *Nature Biotechnology*, vol. 25, 2007.

[17] J. W. M. Bulte, A. H. Schmieder, J. Keupp, S. D. Caruthers, S. A. Wickline, and G. M. Lanza, "MR cholangiography demonstrates unsuspected rapid biliary clearance of nanoparticles in rodents: implications for clinical translation," *Nanomedicine: Nanotechnology, Biology and Medicine*, vol. 10, 2014.

[18] H. S. Choi and J. V. Frangioni, "Nanoparticles for biomedical imaging: fundamentals of clinical translation," *Molecular Imaging*, vol. 9, 2010.

[19] S. Mitragotri and J. Lahann, "Physical approaches to biomaterial design," *Nature Materials*, vol. 8, 2009.

[20] F. Kiessling, M. E. Mertens, J. Grimm, and T. Lammers, "Nanoparticles for imaging: top or flop?," *Radiology*, vol. 273, 2014.

[21] A. N. Lukyanov, W. C. Hartner, and V. P. Torchilin, "Increased accumulation of PEG-PE micelles in the area of experimental myocardial infarction in rabbits," *Journal of Controlled Release*, vol. 94, 2004.

[22] H. Hwang, J. Kwon, P. S. Oh et al., "Peptide-loaded nanoparticles and radionuclide imaging for individualized treatment of myocardial ischemia," *Radiology*, vol. 273, 2014.

[23] G. Fullstone, J. Wood, M. Holcombe, and G. Battaglia, "Modelling the transport of nanoparticles under blood flow using an agent-based approach," *Scientific Reports*, vol. 5, 2015.

[24] H. Ye, Z. Shen, L. Yu, M. Wei, and Y. Li, "Manipulating nanoparticle transport within blood flow through external forces: an exemplar of mechanics in nanomedicine," *Proceedings of the Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences*, vol. 474, p. 20170845, 2018.

[25] S. Barua and S. Mitragotri, "Challenges associated with penetration of nanoparticles across cell and tissue barriers: a review of current status and future prospects," *Nano Today*, vol. 9, 2014.

[26] M. Banach, C. Serban, A. Sahebkar et al., "Impact of statin therapy on coronary plaque composition: a systematic review and meta-analysis of virtual histology intravascular ultrasound studies," *BMC Medicine*, vol. 13, 2015.

[27] N. Kapil, Y. H. Datta, N. Alakbarova et al., "Antiplatelet and anticoagulant therapies for prevention of ischemic stroke," *Clinical and Applied Thrombosis/Hemostasis*, vol. 23, pp. 301–318, 2017.

[28] R. A. Harrington, P. K. Hodgson, and R. L. Larsen, "Antiplatelet therapy," *Circulation*, p. 108, 2003.

[29] T. Geisler, H. Langer, M. Wydymus et al., "Low response to clopidogrel is associated with cardiovascular outcome after coronary stent implantation," *European Heart Journal*, vol. 27, 2006.

[30] S. C. Johnston, J. D. Easton, M. Farrant et al., "Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA," *The New England Journal of Medicine*, vol. 379, pp. 215–225, 2018.

[31] S. Malini, K. Raj, and M. Sennappan, "Electrochemical and spectroscopic studies of interaction of clopidogrel bisulphate with calf thymus DNA," *Asian Journal of Chemistry*, vol. 30, pp. 129–132, 2018.

[32] K. Raj and S. Malini, "Cyclic voltammertic studies of invitro interaction of clopidogrel bisulphate and asprin," *Materials Today: Proceedings*, vol. 5, pp. 22390–22398, 2018.

[33] D. A. Tonetti, B. T. Jankowitz, and B. A. Gross, "Antiplatelet therapy in flow diversion," *Neurosurgery*, p. 86, 2020.

[34] P. Stano, S. Bufali, C. Pisano et al., "Novel camptothecin analogue (gimatecan)-containing liposomes prepared by the ethanol injection method," *Journal of Liposome Research*, vol. 14, 2004.

[35] S. S. K. Dasa, R. Suzuki, M. Gutknecht et al., "Development of target-specific liposomes for delivering small molecule drugs after reperfused myocardial infarction," *Journal of Controlled Release*, vol. 220, 2015.

[36] I. E. Allijn, B. M. S. Czarny, X. Wang et al., "Liposome encapsulated berberine treatment attenuates cardiac dysfunction after myocardial infarction," *Journal of Controlled Release*, vol. 247, 2017.

[37] L. Timmers, J. P. G. Sluijter, J. K. Van Keulen et al., "Toll-like receptor 4 mediates maladaptive left ventricular remodeling and impairs cardiac function after myocardial infarction," *Circulation Research*, vol. 102, 2008.

[38] A. Kumar, V. Hasija, A. Sudhaik et al., "Artificial leaf for light-driven CO2 reduction: basic concepts, advanced structures and selective solar-to-chemical products," *Chemical Engineering Journal*, vol. 430, p. 133031, 2022.

[39] H. N. Cuong, S. Pansambal, S. Ghotekar et al., "New frontiers in the plant extract mediated biosynthesis of copper oxide (CuO) nanoparticles and their potential applications: a review," *Environmental Research*, vol. 203, p. 111858, 2022.

[40] R. Kumar, P. Raizada, A. A. P. Khan et al., "Recent progress in emerging BiPO4-based photocatalysts: synthesis, properties, modification strategies, and photocatalytic applications," *Journal of Materials Science and Technology*, vol. 108, pp. 208–225, 2022.

[41] C. Courts and B. Madea, "Micro-RNA-a potential for forensic science?," *Forensic Science International*, vol. 203, 2010.

[42] J. Wang, W. Huang, R. Xu et al., "MicroRNA-24 regulates cardiac fibrosis after myocardial infarction," *Journal of Cellular and Molecular Medicine*, vol. 16, 2012.

[43] R. J. Perera and A. Ray, "MicroRNAs in the search for understanding human diseases," *BioDrugs*, vol. 21, 2007.

[44] M. Li, X. Tang, X. Liu et al., "Targeted miR-21 loaded liposomes for acute myocardial infarction," *Journal of Materials Chemistry B*, vol. 8, 2020.

[45] A. Al-Darraji, R. R. Donahue, H. Tripathi et al., "Liposomal delivery of azithromycin enhances its immunotherapeutic efficacy and reduces toxicity in myocardial infarction," *Scientific Reports*, vol. 10, 2020.

[46] L. Y. Wei, X. H. Fu, W. Li et al., "Effect of intravenous administration of liposomal prostaglandin E1 on microcirculation in patients with ST elevation myocardial infarction undergoing primary percutaneous intervention," *Chinese Medical Journal*, vol. 128, 2015.

[47] T. Reffelmann and R. A. Kloner, "Microvascular reperfusion injury: rapid expansion of anatomic no reflow during reperfusion in the rabbit," *American Journal of Physiology. Heart and Circulatory Physiology*, vol. 283, 2002.

[48] A. Nakhlband, M. Eskandani, Y. Omidi et al., "Combating atherosclerosis with targeted nanomedicines: recent advances and future prospective," *BioImpacts: BI*, vol. 8, 2018.

[49] F. M. van der Valk, D. F. van Wijk, M. E. Lobatto et al., "Prednisolone-containing liposomes accumulate in human atherosclerotic macrophages upon intravenous administration," *Nanomedicine: Nanotechnology, Biology and Medicine*, vol. 11, 2015.

[50] F. M. van der Valk, D. M. Schulte, S. Meiler et al., "Liposomal prednisolone promotes macrophage lipotoxicity in experimental atherosclerosis," *Nanomedicine: Nanotechnology, Biology and Medicine*, vol. 12, 2016.

[51] "Does the role of angiogenesis play a role in atherosclerosis and plaque instability?," *Anatomy and Physiology*, vol. 4, 2013.

[52] E. A. Kruger and W. D. Figg, "TNP-470: an angiogenesis inhibitor in clinical development for cancer," *Expert Opinion on Investigational Drugs*, vol. 9, 2000.

[53] K. S. Moulton, E. Heller, M. A. Konerding, E. Flynn, W. Palinski, and J. Folkman, "Angiogenesis inhibitors endostatin or TNP-470 reduce intimal neovascularization and plaque growth in apolipoprotein E-deficient mice," *Circulation*, vol. 99, 1999.

[54] I. Pont, A. Calatayud-Pascual, A. López-Castellano et al., "Anti-angiogenic drug loaded liposomes: nanotherapy for early atherosclerotic lesions in mice," *PLoS One*, vol. 13, 2018.

[55] Y. Wu, Y. Zhang, L. L. Dai et al., "An apoptotic body-biomimic liposome in situ upregulates anti-inflammatory macrophages for stabilization of atherosclerotic plaques," *Journal of Controlled Release*, vol. 316, 2019.

[56] N. Zhang, C. Li, D. Zhou et al., "Cyclic RGD functionalized liposomes encapsulating urokinase for thrombolysis," *Acta Biomaterialia*, vol. 70, 2018.

[57] J. Li, F. Ding, X. Qian et al., "Anti-inflammatory cytokine IL10 loaded cRGD liposomes for the targeted treatment of atherosclerosis," *Journal of Microencapsulation*, vol. 38, 2020.

[58] M. E. Lobatto, T. Binderup, P. M. Robson et al., "Multimodal positron emission tomography imaging to quantify uptake of 89Zr-labeled liposomes in the atherosclerotic vessel wall," *Bioconjugate Chemistry*, vol. 31, 2020.

[59] A. Haeri, S. Sadeghian, S. Rabbani, S. Shirani, M. S. Anvari, and S. Dadashzadeh, "Physicochemical characteristics of liposomes are decisive for their antirestenosis efficacy following local delivery," *Nanomedicine*, vol. 12, pp. 131–145, 2017.

[60] L. Ye, H. K. Haider, R. Tan et al., "Angiomyogenesis using liposome based vascular endothelial growth factor-165 transfection with skeletal myoblast for cardiac repair," *Biomaterials*, vol. 29, pp. 2125–2137, 2008.

[61] Y. Qu, J. Tang, L. Liu, L. L. Song, S. Chen, and Y. Gao, "α-Tocopherol liposome loaded chitosan hydrogel to suppress oxidative stress injury in cardiomyocytes," *International Journal of Biological Macromolecules*, vol. 125, pp. 1192–1202, 2019.

[62] M. Ogawa, R. Uchino, A. Kawai, M. Kosugi, and Y. Magata, "PEG modification on 111In-labeled phosphatidyl serine liposomes for imaging of atherosclerotic plaques," *Nuclear Medicine and Biology*, vol. 42, pp. 299–304, 2015.

[63] X. Li, H. Xiao, C. Lin et al., "Synergistic effects of liposomes encapsulating atorvastatin calcium and curcumin and targeting dysfunctional endothelial cells in reducing atherosclerosis," *International Journal of Nanomedicine*, vol. 14, p. 649, 2019.

[64] A. Darwitan, Y. S. Wong, L. T. H. Nguyen et al., "Liposomal nanotherapy for treatment of atherosclerosis," *Advanced Healthcare Materials*, vol. 9, 2020.

[65] E. T. M. Dams, P. Laverman, W. J. G. Oyen et al., "Accelerated blood clearance and altered biodistribution of repeated injections of sterically stabilized liposomes," *The Journal of Pharmacology and Experimental Therapeutics*, vol. 292, no. 3, pp. 1071–1079, 2000.

[66] M. J. Lipinski, J. C. Frias, V. Amirbekian et al., "Macrophage-specific lipid-based nanoparticles improve cardiac magnetic resonance detection and characterization of human atherosclerosis," *JACC: Cardiovascular Imaging*, vol. 2, pp. 637–647, 2009.

[67] B. Alotaibi, E. Tousson, T. A. El-Masry, N. Altwaijry, and A. Saleh, "Ehrlich ascites carcinoma as model for studying the cardiac protective effects of curcumin nanoparticles against cardiac damage in female mice," *Environmental Toxicology*, vol. 36, pp. 105–113, 2021.

[68] F. Pagliari, C. Mandoli, G. Forte et al., "Cerium oxide nanoparticles protect cardiac progenitor cells from oxidative stress," vol. 6, no. 5, pp. 3767–3775, 2012.

[69] S. Y. Tan, C. Teh, C. Y. Ang et al., "Responsive mesoporous silica nanoparticles for sensing of hydrogen peroxide and simultaneous treatment toward heart failure," *Nanoscale*, vol. 9, pp. 2253–2261, 2017.

[70] M. Miragoli, P. Ceriotti, M. Iafisco et al., "Inhalation of peptide-loaded nanoparticles improves heart failure," *Science Translational Medicine*, vol. 10, p. 6205, 2018.

[71] S. Kathiresan, B. F. Voight, S. Purcell et al., "Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants," *Nature Genetics*, vol. 41, pp. 334–341, 2009.

[72] F. K. Swirski and M. Nahrendorf, "Leukocyte behavior in atherosclerosis, myocardial infarction, and heart failure," *Science*, vol. 339, no. 6116, pp. 161–166, 2013.

[73] M. M. Nguyen, A. S. Carlini, M. P. Chien et al., "Enzyme-responsive nanoparticles for targeted accumulation and

prolonged retention in heart tissue after myocardial infarction," *Advanced Materials*, vol. 27, 2015.

[74] Y. Oduk, W. Zhu, R. Kannappan et al., "VEGF nanoparticles repair the heart after myocardial infarction," *American Journal of Physiology. Heart and Circulatory Physiology*, vol. 314, pp. 278–284, 2018.

[75] A. Levin and G. Paret, "Levosimendan," *Journal of Pediatric Intensive Care*, vol. 2, no. 3, pp. 095–103, 2013.

[76] M. Y. Spivak, R. V. Bubnov, I. M. Yemets, L. M. Lazarenko, N. O. Tymoshok, and Z. R. Ulberg, "Development and testing of gold nanoparticles for drug delivery and treatment of heart failure: a theranostic potential for PPP cardiology," *The EPMA Journal*, vol. 4, 2013.

[77] M. P. A. Ferreira, S. Ranjan, S. Kinnunen et al., "Drug-loaded multifunctional nanoparticles targeted to the endocardial layer of the injured heart modulate hypertrophic signaling," *Small*, vol. 13, p. 1701276, 2017.

[78] K. S. Oh, J. Y. Song, S. J. Yoon, Y. Park, D. Kim, and S. H. Yuk, "Temperature-induced gel formation of core/shell nanoparticles for the regeneration of ischemic heart," *Journal of Controlled Release*, vol. 146, no. 2, pp. 207–211, 2010.

[79] S. Liu, X. Chen, L. Bao et al., "Treatment of infarcted heart tissue via the capture and local delivery of circulating exosomes through antibody-conjugated magnetic nanoparticles," *Nature Biomedical Engineering*, vol. 4, no. 11, pp. 1063–1075, 2020.

[80] C. Hu, R. Luo, and Y. Wang, "Heart valves cross-linked with erythrocyte membrane drug-loaded nanoparticles as a biomimetic strategy for anti-coagulation, anti-inflammation, anti-calcification, and endothelialization," *ACS Applied Materials & Interfaces*, vol. 12, no. 37, pp. 41113–41126, 2020.

[81] G. Torrieri, F. Fontana, P. Figueiredo et al., "Dual-peptide functionalized acetalated dextran-based nanoparticles for sequential targeting of macrophages during myocardial infarction," *Nanoscale*, vol. 12, no. 4, pp. 2350–2358, 2020.

[82] J. Qin, Z. Peng, B. Li et al., "Gold nanorods as a theranostic platform for in vitro and in vivo imaging and photothermal therapy of inflammatory macrophages," *Nanoscale*, vol. 7, no. 33, pp. 13991–14001, 2015.

[83] H. Taghavi, M. Bakhshandeh, A. Montazerabadi, H. N. Moghadam, S. B. M. Shahri, and M. Keshtkar, "Comparison of gold nanoparticles and iodinated contrast media in radiation dose reduction and contrast enhancement in computed tomography," *Iranian Journal of Radiology*, vol. 17, no. 1, 2020.

[84] V. Bagalkot, M. A. Badgeley, T. Kampfrath, J. A. Deiuliis, S. Rajagopalan, and A. Maiseyeu, "Hybrid nanoparticles improve targeting to inflammatory macrophages through phagocytic signals," *Journal of Controlled Release*, vol. 217, pp. 243–255, 2015.

[85] Y. H. Ma, S. Y. Wu, T. Wu, Y. J. Chang, M. Y. Hua, and J. P. Chen, "Magnetically targeted thrombolysis with recombinant tissue plasminogen activator bound to polyacrylic acid-coated nanoparticles," *Biomaterials*, vol. 30, no. 19, pp. 3343–3351, 2009.

[86] H. W. Yang, M. Y. Hua, K. J. Lin et al., "Bioconjugation of recombinant tissue plasminogen activator to magnetic nanocarriers for targeted thrombolysis," *International Journal of Nanomedicine*, vol. 7, pp. 5159–5173, 2012.

[87] J. Zhou, D. Guo, Y. Zhang, W. Wu, H. Ran, and Z. Wang, "Construction and evaluation of Fe_3O_4-based PLGA nanoparticles carrying rtPA used in the detection of thrombosis and in targeted thrombolysis," *ACS Applied Materials & Interfaces*, vol. 6, no. 8, pp. 5566–5576, 2014.

[88] G. Huang, Z. Zhou, R. Srinivasan et al., "Affinity manipulation of surface-conjugated RGD peptide to modulate binding of liposomes to activated platelets," *Biomaterials*, vol. 29, no. 11, pp. 1676–1685, 2008.

[89] D. B. Cowan, R. Yao, V. Akurathi et al., "Intracoronary delivery of mitochondria to the ischemic heart for cardioprotection," *PLoS One*, vol. 11, no. 8, p. e0160889, 2016.

[90] J. D. McCully, D. B. Cowan, C. A. Pacak, I. K. Toumpoulis, H. Dayalan, and S. Levitsky, "Injection of isolated mitochondria during early reperfusion for cardioprotection," *American Journal of Physiology. Heart and Circulatory Physiology*, vol. 296, no. 1, pp. H94–H105, 2009.

[91] A. Masuzawa, K. M. Black, C. A. Pacak et al., "Transplantation of autologously derived mitochondria protects the heart from ischemia-reperfusion injury," *American Journal of Physiology. Heart and Circulatory Physiology*, vol. 304, no. 7, pp. H966–H982, 2013.

[92] M. Chandarana, A. Curtis, and C. Hoskins, "The use of nanotechnology in cardiovascular disease," *Applied Nanoscience*, vol. 8, no. 7, pp. 1607–1619, 2018.

[93] S. Katsuki, T. Matoba, J. I. Koga, K. Nakano, and K. Egashira, "Anti-inflammatory nanomedicine for cardiovascular disease," *Frontiers in Cardiovascular Medicine*, vol. 4, 2017.

[94] M. P. A. Ferreira, V. Talman, G. Torrieri et al., "Dual-drug delivery using dextran-functionalized nanoparticles targeting cardiac fibroblasts for cellular reprogramming," *Advanced Functional Materials*, vol. 28, no. 15, 2018.

[95] M. Giannouli, V. Karagkiozaki, F. Pappa, I. Moutsios, C. Gravalidis, and S. Logothetidis, "Fabrication of quercetin-loaded PLGA nanoparticles via electrohydrodynamic atomization for cardiovascular disease," *Proceedings of the Materials Today: Proceedings*, vol. 5, no. 8, pp. 15998–16005, 2018.

[96] B. L. Banik, P. Fattahi, and J. L. Brown, "Polymeric nanoparticles: the future of nanomedicine," *Wiley Interdisciplinary Reviews. Nanomedicine and Nanobiotechnology*, vol. 8, no. 2, pp. 271–299, 2016.

[97] P. C. Lee, B. S. Zan, L. T. Chen, and T. W. Chung, "Multifunctional PLGA-based nanoparticles as a controlled release drug delivery system for antioxidant and anticoagulant therapy," *International Journal of Nanomedicine*, vol. 14, pp. 1533–1549, 2019.

[98] A. Jayagopal, P. K. Russ, and F. R. Haselton, "Surface engineering of quantum dots for in vivo vascular imaging," *Bioconjugate Chemistry*, vol. 18, no. 5, pp. 1424–1433, 2007.

[99] S. K. Tuteja, R. Chen, M. Kukkar et al., "A label-free electrochemical immunosensor for the detection of cardiac marker using graphene quantum dots (GQDs)," *Biosensors & Bioelectronics*, vol. 86, pp. 548–556, 2016.

[100] M. Galagudza, D. Korolev, V. Postnov et al., "Passive targeting of ischemic-reperfused myocardium with adenosine-loaded silica nanoparticles," *International Journal of Nanomedicine*, vol. 7, 2012.

[101] J. M. Hamilton, D. P. Salmon, D. Galasko et al., "Visuospatial deficits predict rate of cognitive decline in autopsy-verified dementia with Lewy bodies," *Neuropsychology*, vol. 22, no. 6, pp. 729–737, 2008.

[102] J. Sun, S. Wang, D. Zhao, F. H. Hun, L. Weng, and H. Liu, "Cytotoxicity, permeability, and inflammation of metal oxide nanoparticles in human cardiac microvascular endothelial cells: cytotoxicity, permeability, and inflammation of metal oxide nanoparticles," *Cell Biology and Toxicology*, vol. 27, no. 5, pp. 333–342, 2011.

[103] S. C. Hong, J. H. Lee, J. Lee et al., "Subtle cytotoxicity and genotoxicity differences in superparamagnetic iron oxide nanoparticles coated with various functional groups," *International Journal of Nanomedicine*, vol. 6, 2011.

[104] N. K. Iversen, S. Frische, K. Thomsen et al., "Superparamagnetic iron oxide polyacrylic acid coated γ-Fe2O3 nanoparticles do not affect kidney function but cause acute effect on the cardiovascular function in healthy mice," *Toxicology and Applied Pharmacology*, vol. 266, no. 2, pp. 276–288, 2013.

[105] S. Liu, Y. Han, L. Yin, L. Long, and R. Liu, "Toxicology studies of a superparamagnetic iron oxide nanoparticle In Vivo," *Proceedings of the Advanced Materials Research*, vol. 47-50, PART 2, pp. 1097–1100, 2008.

[106] M. Mahmoudi, H. Hofmann, B. Rothen-Rutishauser, and A. Petri-Fink, "Assessing the in vitro and in vivo toxicity of superparamagnetic iron oxide nanoparticles," *Chemical Reviews*, vol. 112, no. 4, pp. 2323–2338, 2012.

[107] M. Khan, Y. Xu, S. Hua et al., "Correction: Evaluation of changes in morphology and function of human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CMs) cultured on an aligned-nanofiber cardiac patch," *PLoS One*, vol. 10, no. 10, p. e0141176, 2015.

[108] S. Pok, J. D. Myers, S. V. Madihally, and J. G. Jacot, "A multilayered scaffold of a chitosan and gelatin hydrogel supported by a PCL core for cardiac tissue engineering," *Acta Biomaterialia*, vol. 9, no. 3, pp. 5630–5642, 2013.

[109] Y. Wu, L. Wang, B. Guo, and P. X. Ma, "Interwoven aligned conductive nanofiber yarn/hydrogel composite scaffolds for engineered 3D cardiac anisotropy," *ACS Nano*, vol. 11, no. 6, pp. 5646–5659, 2017.

[110] R. Lakshmanan, P. Kumaraswamy, U. M. Krishnan, and S. Sethuraman, "Engineering a growth factor embedded nanofiber matrix niche to promote vascularization for functional cardiac regeneration," *Biomaterials*, vol. 97, pp. 176–195, 2016.

[111] M. Ding, H. Andersson, S. Martinsson et al., "Aligned nanofiber scaffolds improve functionality of cardiomyocytes differentiated from human induced pluripotent stem cell-derived cardiac progenitor cells," *Scientific Reports*, vol. 10, no. 1, p. 13575, 2020.

[112] B. W. Streeter, J. Xue, Y. Xia, and M. E. Davis, "Electrospun nanofiber-based patches for the delivery of cardiac progenitor cells," *ACS Applied Materials & Interfaces*, vol. 11, no. 20, pp. 18242–18253, 2019.

[113] B. J. Kang, H. Kim, S. K. Lee et al., "Umbilical-cord-blood-derived mesenchymal stem cells seeded onto fibronectin-immobilized polycaprolactone nanofiber improve cardiac function," *Acta Biomaterialia*, vol. 10, no. 7, pp. 3007–3017, 2014.

[114] A. Kumar, A. Patel, L. Duvalsaint, M. Desai, and E. D. Marks, "Thymosin β4 coated nanofiber scaffolds for the repair of damaged cardiac tissue," *Journal of Nanobiotechnology*, vol. 12, no. 1, p. 10, 2014.

[115] M. M. Sayed, H. M. Mousa, M. R. El-Aassar et al., "Enhancing mechanical and biodegradation properties of polyvinyl alcohol/silk fibroin nanofibers composite patches for cardiac tissue engineering," *Materials Letters*, vol. 255, p. 126510, 2019.

[116] H. M. Mousa, K. H. Hussein, M. M. Sayed et al., "Development of biocompatible tri-layered nanofibers patches with endothelial cells for cardiac tissue engineering," *European Polymer Journal*, vol. 129, p. 109630, 2020.

[117] A. J. Rufaihah, I. C. Yasa, V. S. Ramanujam et al., "Angiogenic peptide nanofibers repair cardiac tissue defect after myocardial infarction," *Acta Biomaterialia*, vol. 58, pp. 102–112, 2017.

[118] S. M. Dallabrida, N. Ismail, J. R. Oberle, B. E. Himes, and M. A. Rupnick, "Angiopoietin-1 promotes cardiac and skeletal myocyte survival through integrins," *Circulation Research*, vol. 96, no. 4, pp. e8–24, 2005.

[119] J. M. Tang, J. N. Wang, L. Zhang et al., "VEGF/SDF-1 promotes cardiac stem cell mobilization and myocardial repair in the infarcted heart," *Cardiovascular Research*, vol. 91, no. 3, pp. 402–411, 2011.

[120] S. Shojaie, M. Rostamian, A. Samadi et al., "Electrospun electroactive nanofibers of gelatin-oligoaniline/Poly (vinyl alcohol) templates for architecting of cardiac tissue with on-demand drug release," *Polymers for Advanced Technologies*, vol. 30, no. 6, pp. 1473–1483, 2019.

[121] H. Nazari, A. Heirani-Tabasi, M. Hajiabbas et al., "Incorporation of two-dimensional nanomaterials into silk fibroin nanofibers for cardiac tissue engineering," *Polymers for Advanced Technologies*, vol. 31, no. 2, pp. 248–259, 2020.

[122] H. Nazari, A. Heirani-Tabasi, M. Hajiabbas et al., "Incorporation of SPION-casein core-shells into silk-fibroin nanofibers for cardiac tissue engineering," *Journal of Cellular Biochemistry*, vol. 121, no. 4, pp. 2981–2993, 2020.

[123] A. Ghasemi, R. Imani, M. Yousefzadeh, S. Bonakdar, A. Solouk, and H. Fakhrzadeh, "Studying the potential application of electrospun polyethylene terephthalate/graphene oxide nanofibers as electroconductive cardiac patch," *Macromolecular Materials and Engineering*, vol. 304, no. 8, p. 1900187, 2019.

[124] H. A. Kassam, D. C. Gillis, B. R. Dandurand et al., "Development of fractalkine-targeted nanofibers that localize to sites of arterial injury," *Nanomaterials*, vol. 10, no. 3, p. 420, 2020.

[125] M. Suhaeri, R. Subbiah, S. H. Kim et al., "Novel platform of cardiomyocyte culture and coculture via fibroblast-derived matrix-coupled aligned electrospun nanofiber," *ACS Applied Materials & Interfaces*, vol. 9, no. 1, pp. 224–235, 2017.

[126] H. Liao, R. Qi, M. Shen et al., "Improved cellular response on multiwalled carbon nanotube-incorporated electrospun polyvinyl alcohol/chitosan nanofibrous scaffolds," *Colloids and Surfaces. B, Biointerfaces*, vol. 84, no. 2, pp. 528–535, 2011.

[127] A. M. Wickham, M. M. Islam, D. Mondal et al., "Polycaprolactone-thiophene-conjugated carbon nanotube meshes as scaffolds for cardiac progenitor cells," *Journal of Biomedical Materials Research – Part B: Applied Biomaterials*, vol. 102, no. 7, pp. 1553–1561, 2014.

[128] M. Kharaziha, S. R. Shin, M. Nikkhah et al., "Tough and flexible CNT-polymeric hybrid scaffolds for engineering cardiac constructs," *Biomaterials*, vol. 35, no. 26, pp. 7346–7354, 2014.

[129] D. A. Stout, B. Basu, and T. J. Webster, "Poly (lactic-co-glycolic acid): carbon nanofiber composites for myocardial tissue engineering applications," *Acta Biomaterialia*, vol. 7, no. 8, pp. 3101–3112, 2011.

[130] X. Meng, D. A. Stout, L. Sun, R. L. Beingessner, H. Fenniri, and T. J. Webster, "Novel injectable biomimetic hydrogels with carbon nanofibers and self assembled rosette nanotubes for myocardial applications," *Journal of Biomedical Materials Research Part A*, vol. 101A, no. 4, pp. 1095–1102, 2013.

[131] Q. Liu, S. Tian, C. Zhao et al., "Porous nanofibrous poly (l-lactic acid) scaffolds supporting cardiovascular progenitor cells for cardiac tissue engineering," *Acta Biomaterialia*, vol. 26, pp. 105–114, 2015.

[132] R. M. Aghdam, S. Shakhesi, S. Najarian, M. M. Mohammadi, S. H. Ahmadi Tafti, and H. Mirzadeh, "Fabrication of a nanofibrous scaffold for the in vitro culture of cardiac progenitor cells for myocardial regeneration," *International Journal of Polymeric Materials and Polymeric Biomaterials*, vol. 63, no. 5, pp. 229–239, 2014.

[133] R. Amezcua, A. Shirolkar, C. Fraze, and D. A. Stout, "Nanomaterials for cardiac myocyte tissue engineering," *Nanomaterials*, vol. 6, no. 7, p. 133, 2016.

[134] K. Ashtari, H. Nazari, H. Ko et al., "Electrically conductive nanomaterials for cardiac tissue engineering," *Advanced Drug Delivery Reviews*, vol. 144, pp. 162–179, 2019.

[135] L. Li, Y. Wang, R. Guo et al., "Ginsenoside Rg3-loaded, reactive oxygen species-responsive polymeric nanoparticles for alleviating myocardial ischemia-reperfusion injury," *Journal of Controlled Release*, vol. 317, pp. 259–272, 2020.

[136] C. Cristallini, G. Vaccari, N. Barbani et al., "Cardioprotection of PLGA/gelatine cardiac patches functionalised with adenosine in a large animal model of ischaemia and reperfusion injury: a feasibility study," *Journal of Tissue Engineering and Regenerative Medicine*, vol. 13, no. 7, pp. 1253–1264, 2019.

[137] C. Cristallini, C. Giachino, N. Barbani, E. C. Rocchietti, M. Gagliardi, and P. Pagliaro, "A polymeric scaffold for cardiac regeneration and protection from reperfusion injury-WO2014108814A1," Google Patent.

[138] C. Cristallini, M. Gagliardi, N. Barbani, D. Giannessi, and G. D. Guerra, "Novel biodegradable, biomimetic and functionalised polymer scaffolds to prevent expansion of post-infarct left ventricular remodelling," *Journal of Materials Science. Materials in Medicine*, vol. 23, no. 1, pp. 205–216, 2012.

[139] P. C. Sherrell, A. Cieślar-Pobuda, M. S. Ejneby et al., "Rational design of a conductive collagen heart patch," *Macromolecular Bioscience*, vol. 17, no. 7, 2017.

[140] B. Peña, S. Bosi, B. A. Aguado et al., "Injectable Carbon Nanotube-Functionalized Reverse Thermal Gel Promotes Cardiomyocytes Survival and Maturation," *ACS Applied Materials & Interfaces*, vol. 9, no. 37, pp. 31645–31656, 2017.

[141] J. Ren, Q. Xu, X. Chen et al., "Superaligned carbon nanotubes guide oriented cell growth and promote electrophysiological homogeneity for synthetic cardiac tissues," *Advanced Materials*, vol. 29, no. 44, 2017.

[142] M. D. Mccauley, F. Vitale, J. S. Yan et al., "In vivo restoration of myocardial conduction with carbon nanotube fibers," *Circulation. Arrhythmia and Electrophysiology*, vol. 12, no. 8, p. e007256, 2019.

[143] M. Tashakori-Miyanroudi, K. Rakhshan, M. Ramez et al., "Conductive carbon nanofibers incorporated into collagen bio-scaffold assists myocardial injury repair," *International Journal of Biological Macromolecules*, vol. 163, pp. 1136–1146, 2020.

[144] B. Ataei, M. T. Khorasani, M. Karimi, and M. Daliri-Joupari, "Plasma modification of heparinised CNT/PU nanocomposite and measuring of mechanical, calcification and platelet adhesion properties for application in heart valve," *Plastics, Rubber and Composites*, vol. 49, no. 7, pp. 289–299, 2020.

[145] J. T. T. Angelina, S. Ganesan, T. M. R. Panicker, R. Narayani, M. Paul Korath, and K. Jagadeesan, "Pulsed laser deposition of silver nanoparticles on prosthetic heart valve material to prevent bacterial infection," *Materials and Technologies*, vol. 32, no. 3, pp. 148–155, 2017.

[146] S. Ahadian, L. Davenport Huyer, M. Estili et al., "Moldable elastomeric polyester-carbon nanotube scaffolds for cardiac tissue engineering," *Acta Biomaterialia*, vol. 52, pp. 81–91, 2017.

[147] A. M. Martins, G. Eng, S. G. Caridade, J. F. Mano, R. L. Reis, and G. Vunjak-Novakovic, "Electrically conductive chitosan/carbon scaffolds for cardiac tissue engineering," *Biomacromolecules*, vol. 15, no. 2, pp. 635–643, 2014.

[148] S. R. Shin, C. Zihlmann, M. Akbari et al., "Reduced graphene oxide-GelMA hybrid hydrogels as scaffolds for cardiac tissue engineering," *Small*, vol. 12, no. 27, pp. 3677–3689, 2016.

[149] S. Rastegar, M. Mehdikhani, A. Bigham, E. Poorazizi, and M. Rafienia, "Poly glycerol sebacate/polycaprolactone/carbon quantum dots fibrous scaffold as a multifunctional platform for cardiac tissue engineering," *Materials Chemistry and Physics*, vol. 266, p. 124543, 2021.

[150] P. Ahmadi, N. Nazeri, M. A. Derakhshan, and H. Ghanbari, "Preparation and characterization of polyurethane/chitosan/CNT nanofibrous scaffold for cardiac tissue engineering," *International Journal of Biological Macromolecules*, vol. 180, pp. 590–598, 2021.

[151] C. Yan, Y. Ren, X. Sun et al., "Photoluminescent functionalized carbon quantum dots loaded electroactive silk fibroin/PLA nanofibrous bioactive scaffolds for cardiac tissue engineering," *Journal of Photochemistry and Photobiology B: Biology*, vol. 202, p. 111680, 2020.

[152] S. Mombini, J. Mohammadnejad, B. Bakhshandeh et al., "Chitosan-PVA-CNT nanofibers as electrically conductive scaffolds for cardiovascular tissue engineering," *International Journal of Biological Macromolecules*, vol. 140, pp. 278–287, 2019.

[153] H. Sun, J. Tang, Y. Mou et al., "Carbon nanotube-composite hydrogels promote intercalated disc assembly in engineered cardiac tissues through β1-integrin mediated FAK and RhoA pathway," *Acta Biomaterialia*, vol. 48, pp. 88–99, 2017.

[154] M. Cabiati, F. Vozzi, F. Gemma et al., "Cardiac tissue regeneration: a preliminary study on carbon-based nanotubes gelatin scaffold," *Journal of Biomedical Materials Research – Part B: Applied Biomaterials*, vol. 106, no. 8, pp. 2750–2762, 2018.

[155] K. Roshanbinfar, J. Hilborn, O. P. Varghese, and O. P. Oommen, "Injectable and thermoresponsive pericardial matrix derived conductive scaffold for cardiac tissue engineering," *RSC Advances*, vol. 7, no. 51, pp. 31980–31988, 2017.

[156] C. M. B. Ho, A. Mishra, P. T. P. Lin et al., "3D printed polycaprolactone carbon nanotube composite scaffolds for cardiac tissue engineering," *Macromolecular Bioscience*, vol. 17, no. 4, 2017.

[157] D. Kaya, K. Küçükada, and N. Alemdar, "Modeling the drug release from reduced graphene oxide-reinforced hyaluronic acid/gelatin/poly (ethylene oxide) polymeric films," *Carbohydrate Polymers*, vol. 215, pp. 189–197, 2019.

[158] G. Sarkar, N. R. Saha, I. Roy et al., "Cross-linked methyl cellulose/graphene oxide rate controlling membranes for:

in vitro and ex vivo permeation studies of diltiazem hydrochloride," *RSC Advances*, vol. 6, no. 42, pp. 36136–36145, 2016.

[159] A. Masotti, M. R. Miller, A. Celluzzi et al., "Regulation of angiogenesis through the efficient delivery of microRNAs into endothelial cells using polyamine-coated carbon nanotubes," *Nanomedicine: Nanotechnology, Biology and Medicine*, vol. 12, no. 6, pp. 1511–1522, 2016.

[160] A. Paul, W. Shao, D. Shum-Tim, and S. Prakash, "The attenuation of restenosis following arterial gene transfer using carbon nanotube coated stent incorporating TAT/DNAAng1 +Vegf nanoparticles," *Biomaterials*, vol. 33, no. 30, pp. 7655–7664, 2012.

[161] R. Zhang and H. Olin, "Carbon nanomaterials as drug carriers: real time drug release investigation," *Materials Science and Engineering: C*, vol. 32, no. 5, pp. 1247–1252, 2012.

[162] A. B. Seabra, A. J. Paula, R. De Lima, O. L. Alves, and N. Durán, "Nanotoxicity of graphene and graphene oxide," *Chemical Research in Toxicology*, vol. 27, no. 2, pp. 159–168, 2014.

[163] T. P. Dasari Shareena, D. McShan, A. K. Dasmahapatra, and P. B. Tchounwou, "A review on graphene-based nanomaterials in biomedical applications and risks in environment and health," *Nano-Micro Letters*, vol. 10, no. 3, p. 53, 2018.

[164] H. B. Bostan, R. Rezaee, M. G. Valokala et al., "Cardiotoxicity of nano-particles," *Life Sciences*, vol. 165, pp. 91–99, 2016.

[165] M. C. Duch, G. R. S. Budinger, Y. T. Liang et al., "Minimizing oxidation and stable nanoscale dispersion improves the biocompatibility of graphene in the lung," *Nano Letters*, vol. 11, no. 12, pp. 5201–5207, 2011.

[166] Z. Chen, C. Yu, I. A. Khan, Y. Tang, S. Liu, and M. Yang, "Toxic effects of different-sized graphene oxide particles on zebrafish embryonic development," *Ecotoxicology and Environmental Safety*, vol. 197, p. 110608, 2020.

[167] H. Tong, J. K. McGee, R. K. Saxena, U. P. Kodavanti, R. B. Devlin, and M. I. Gilmour, "Influence of acid functionalization on the cardiopulmonary toxicity of carbon nanotubes and carbon black particles in mice," *Toxicology and Applied Pharmacology*, vol. 239, no. 3, pp. 224–232, 2009.

[168] V. M. Harik, "Geometry of carbon nanotubes and mechanisms of phagocytosis and toxic effects," *Toxicology Letters*, vol. 273, pp. 69–85, 2017.

[169] H. L. Crampton and E. E. Simanek, "Dendrimers as drug delivery vehicles: non-covalent interactions of bioactive compounds with dendrimers," *Polymer International*, vol. 56, no. 4, pp. 489–496, 2007.

[170] A. P. Sherje, M. Jadhav, B. R. Dravyakar, and D. Kadam, "Dendrimers: a versatile nanocarrier for drug delivery and targeting," *International Journal of Pharmaceutics*, vol. 548, no. 1, pp. 707–720, 2018.

[171] L. P. Mendes, J. Pan, and V. P. Torchilin, "Dendrimers as nanocarriers for nucleic acid and drug delivery in cancer therapy," *Molecules*, vol. 22, no. 9, p. 1401, 2017.

[172] W. D. Jang and T. Aida, "Dendritic physical gels: structural parameters for gelation with peptide-core dendrimers," *Macromolecules*, vol. 36, no. 22, pp. 8461–8469, 2003.

[173] C. Napoli, F. de Nigris, S. Williams-Ignarro, O. Pignalosa, V. Sica, and L. J. Ignarro, "Nitric oxide and atherosclerosis: an update," *Nitric Oxide: Biology and Chemistry*, vol. 15, no. 4, pp. 265–279, 2006.

[174] Y. Lu, B. Sun, C. Li, and M. H. Schoenfisch, "Structurally diverse nitric oxide-releasing poly (propylene imine) dendrimers," *Chemistry of Materials*, vol. 23, no. 18, pp. 4227–4233, 2011.

[175] A. Gothwal, P. Kesharwani, U. Gupta et al., "Dendrimers as an effective nanocarrier in cardiovascular disease," *Current Pharmaceutical Design*, vol. 21, no. 30, pp. 4519–4526, 2015.

[176] H. Türk, A. Shukla, P. C. A. Rodrigues, H. Rehage, and R. Haag, "Water-soluble dendritic core-shell-type architectures based on polyglycerol for solubilization of hydrophobic drugs," *Chemistry - A European Journal*, vol. 13, no. 15, pp. 4187–4196, 2007.

[177] N. K. Egilmez, Y. Iwanuma, and R. B. Bankert, "Evaluation and optimization of different cationic liposome formulations for in vivo gene transfer," *Biochemical and Biophysical Research Communications*, vol. 221, no. 1, pp. 169–173, 1996.

[178] H. San, Z. Y. Yang, V. J. Pompili et al., "Safety and short-term toxicity of a novel cationic lipid formulation for human gene therapy," *Human Gene Therapy*, vol. 4, no. 6, pp. 781–788, 1993.

[179] E. G. Nabel, G. Plautz, and G. J. Nabel, "Site-specific gene expression in vivo by direct gene transfer into the arterial wall," *Science*, vol. 249, no. 4974, pp. 1285–1288, 1990.

[180] H. Lin, M. S. Parmacek, G. Morle, S. Bolling, and J. M. Leiden, "Expression of recombinant genes in myocardium in vivo after direct injection of DNA," *Circulation*, vol. 82, no. 6, pp. 2217–2221, 1990.

[181] L. Qin, D. R. Pahud, Y. Ding et al., "Efficient transfer of genes into murine cardiac grafts by starburst polyamidoamine dendrimers," *Human Gene Therapy*, vol. 9, no. 4, pp. 553–560, 1998.

[182] M. P. Turunen, M. O. Hiltunen, M. Ruponen et al., "Efficient adventitial gene delivery to rabbit carotid artery with cationic polymer-plasmid complexes," *Gene Therapy*, vol. 6, no. 1, pp. 6–11, 1999.

[183] Y. Wang, P. Boros, J. Liu et al., "DNA/dendrimer complexes mediate gene transfer into murine cardiac transplants ex vivo," *Molecular Therapy*, vol. 2, no. 6, pp. 602–608, 2000.

[184] Y. Wang, Y. Bai, C. Price et al., "Combination of electroporation and DNA/dendrimer complexes enhances gene transfer into murine cardiac transplants," *American Journal of Transplantation*, vol. 1, no. 4, pp. 334–338, 2001.

[185] S. Theoharis, U. Krueger, P. H. Tan, D. O. Haskard, M. Weber, and A. J. T. George, "Targeting gene delivery to activated vascular endothelium using anti E/P-Selectin antibody linked to PAMAM dendrimers," *Journal of Immunological Methods*, vol. 343, 2009.

[186] K. Jain, P. Kesharwani, U. Gupta, and N. K. Jain, "Dendrimer toxicity: let's meet the challenge," *International Journal of Pharmaceutics*, vol. 394, no. 1-2, pp. 122–142, 2010.

[187] C. M. J. Hu, L. Zhang, S. Aryal, C. Cheung, R. H. Fang, and L. Zhang, "Erythrocyte membrane-camouflaged polymeric nanoparticles as a biomimetic delivery platform," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 108, no. 27, pp. 10980–10985, 2011.

[188] Y. Wang, K. Zhang, X. Qin et al., "Biomimetic nanotherapies: red blood cell based core–shell structured nanocomplexes for atherosclerosis management," *Advancement of Science*, vol. 6, no. 12, 2019.

[189] C. M. J. Hu, R. H. Fang, K. C. Wang et al., "Nanoparticle biointerfacing by platelet membrane cloaking," *Nature*, vol. 526, no. 7571, pp. 118–121, 2015.

[190] S. Wang, R. Wang, N. Meng et al., "Platelet membrane-functionalized nanoparticles with improved targeting ability and lower hemorrhagic risk for thrombolysis therapy," *Journal of Controlled Release*, vol. 328, pp. 78–86, 2020.

[191] Y. Zhao, R. Xie, N. Yodsanit et al., "Hydrogen peroxide-responsive platelet membrane-coated nanoparticles for thrombus therapy," *Biomaterials Science*, vol. 9, no. 7, pp. 2696–2708, 2021.

[192] P. Y. Fang, L. M. G. Ramos, S. Y. Holguin et al., "Functional RNAs: combined assembly and packaging in VLPs," *Nucleic Acids Research*, vol. 45, no. 6, pp. 3519–3527, 2017.

[193] B. K. Gan, C. Y. Yong, K. L. Ho, A. R. Omar, N. B. Alitheen, and W. S. Tan, "Targeted delivery of cell penetrating peptide virus-like nanoparticles to skin cancer cells," *Scientific Reports*, vol. 8, no. 1, pp. 1–3, 2018.

[194] H. Kim, H. Choi, Y. Bae, and S. Kang, "Development of target-tunable P22 VLP-based delivery nanoplatforms using bacterial superglue," *Biotechnology and Bioengineering*, vol. 116, no. 11, pp. 2843–2851, 2019.

[195] L. Zhao, M. Kopylov, C. S. Potter, B. Carragher, and M. G. Finn, "Engineering the PP7 virus capsid as a peptide display platform," *ACS Nano*, vol. 13, no. 4, pp. 4443–4454, 2019.

[196] Y. Ren, Y. Mu, L. Jiang et al., "Multifunctional TK-VLPs nanocarrier for tumor-targeted delivery," *International Journal of Pharmaceutics*, vol. 502, no. 1-2, pp. 249–257, 2016.

[197] J. S. Santillán-Uribe, J. Valadez-García, A. . C. Morán-García, H. C. Santillán-Uribe, and I. Bustos-Jaimes, "Peptide display on a surface loop of human parvovirus B19 VP2: assembly and characterization of virus-like particles," *Virus Research*, vol. 201, pp. 1–7, 2015.

[198] X. Sun, W. Li, X. Zhang et al., "In vivo targeting and imaging of atherosclerosis using multifunctional virus-like particles of Simian virus 40," *Nano Letters*, vol. 16, no. 10, pp. 6164–6171, 2016.

[199] M. Mahmoudi, I. Lynch, M. R. Ejtehadi, M. P. Monopoli, F. B. Bombelli, and S. Laurent, "Protein-nanoparticle interactions: opportunities and challenges," *Chemical Reviews*, vol. 111, no. 9, pp. 5610–5637, 2011.

[200] M. P. Monopoli, D. Walczyk, A. Campbell et al., "Physical-chemical aspects of protein corona: relevance to in vitro and in vivo biological impacts of nanoparticles," *Journal of the American Chemical Society*, vol. 133, no. 8, pp. 2525–2534, 2011.

[201] W. Xiao and H. Gao, "The impact of protein corona on the behavior and targeting capability of nanoparticle-based delivery system," *International Journal of Pharmaceutics*, vol. 552, no. 1-2, pp. 328–339, 2018.

[202] M. P. Monopoli, C. Åberg, A. Salvati, and K. A. Dawson, "Biomolecular coronas provide the biological identity of nanosized materials," *Nature Nanotechnology*, vol. 7, no. 12, pp. 779–786, 2012.

[203] V. Mirshafiee, M. Mahmoudi, K. Lou, J. Cheng, and M. L. Kraft, "Protein corona significantly reduces active targeting yield," *Chemical Communications*, vol. 49, 2013.

[204] A. Salvati, A. S. Pitek, M. P. Monopoli et al., "Transferrin-functionalized nanoparticles lose their targeting capabilities when a biomolecule corona adsorbs on the surface," *Nature Nanotechnology*, vol. 8, 2013.

[205] D. F. Moyano, K. Saha, G. Prakash et al., "Fabrication of corona-free nanoparticles with tunable hydrophobicity," *ACS Nano*, vol. 8, 2014.

[206] S. J. Dixon, K. M. Lemberg, M. R. Lamprecht et al., "Ferroptosis: an iron-dependent form of nonapoptotic cell death," *Cell*, vol. 149, no. 5, pp. 1060–1072, 2012.

[207] S. J. Dixon and B. R. Stockwell, "The role of iron and reactive oxygen species in cell death," *Nature Chemical Biology*, vol. 10, no. 1, pp. 9–17, 2014.

[208] W. G. Kreyling, A. M. Abdelmonem, Z. Ali et al., "In vivo integrity of polymer-coated gold nanoparticles," *Nature Nanotechnology*, vol. 10, 2015.

[209] F. Dilnawaz, S. Acharya, and S. K. Sahoo, "Recent trends of nanomedicinal approaches in clinics," *International Journal of Pharmaceutics*, vol. 538, no. 1-2, pp. 263–278, 2018.

[210] K. Riehemann, S. W. Schneider, T. A. Luger, B. Godin, M. Ferrari, and H. Fuchs, "Nanomedicine-challenge and perspectives," *Angewandte Chemie, International Edition*, vol. 48, no. 5, pp. 872–897, 2009.

[211] J. A. Jackman, T. Mészáros, T. Fülöp, R. Urbanics, J. Szebeni, and N. J. Cho, "Comparison of complement activation-related pseudoallergy in miniature and domestic pigs: foundation of a validatable immune toxicity model," *Nanomedicine: Nanotechnology, Biology and Medicine*, vol. 12, 2016.

[212] J. Szebeni and G. Storm, "Complement activation as a bioequivalence issue relevant to the development of generic liposomes and other nanoparticulate drugs," *Biochemical and Biophysical Research Communications*, vol. 468, 2015.

[213] S. Hua, M. B. C. de Matos, J. M. Metselaar, and G. Storm, "Current trends and challenges in the clinical translation of nanoparticulate nanomedicines: pathways for translational development and commercialization," *Frontiers in Pharmacology*, vol. 9, 2018.

[214] V. Sainz, J. Conniot, A. I. Matos et al., "Regulatory aspects on nanomedicines," *Biochemical and Biophysical Research Communications*, vol. 468, no. 3, pp. 504–510, 2015.

[215] R. Gaspar, "Regulatory issues surrounding nanomedicines: setting the scene for the next generation of nanopharmaceuticals," *Nanomedicine*, vol. 2, 2007.

[216] J. I. Hare, T. Lammers, M. B. Ashford, S. Puri, G. Storm, and S. T. Barry, "Challenges and strategies in anti-cancer nanomedicine development: an industry perspective," *Advanced Drug Delivery Reviews*, vol. 108, pp. 25–38, 2017.

[217] L. Accomasso, C. Cristallini, and C. Giachino, "Risk assessment and risk minimization in nanomedicine: a need for predictive, alternative, and 3Rs strategies," *Frontiers in Pharmacology*, vol. 9, p. 228, 2018.

[218] H. Chopra, S. Kumar, and I. Singh, "Bioinks for 3D printing of artificial extracellular matrices," in *Advanced 3D-Printed Systems and Nanosystems for Drug Delivery and Tissue Engineering*, pp. 1–37, Elsevier, 2020.

[219] J. Kanawati, A. J. Kanawati, M. K. Rowe, H. Khan, W. K. Chan, and R. Yee, "Utility of 3-D printing for cardiac resynchronization device implantation in congenital heart disease," *Heart. Case Reports*, vol. 6, 2020.

[220] N. Tiwari, H. R. Ramamurthy, V. Kumar, A. Kumar, B. Dhanalakshmi, and G. Kumar, "The role of three-dimensional printed cardiac models in the management of complex congenital heart diseases," *Medical Journal, Armed Forces India*, vol. 77, no. 3, pp. 322–330, 2021.

[221] B. Rezaei, A. M. Shoushtari, M. Rabiee, L. Uzun, W. C. Mak, and A. P. F. Turner, "An electrochemical immunosensor for cardiac Troponin I using electrospun carboxylated multi-

walled carbon nanotube-whiskered nanofibres," *Talanta*, vol. 182, 2018.

[222] L. Wang, W. Dou, J. Chen et al., "A CNT-PDMS wearable device for simultaneous measurement of wrist pulse pressure and cardiac electrical activity," *Materials Science and Engineering: C*, vol. 117, 2020.

[223] X. Song, X. Wang, J. Zhang et al., "A tunable self-healing ionic hydrogel with microscopic homogeneous conductivity as a cardiac patch for myocardial infarction repair," *Biomaterials*, vol. 273, 2021.

[224] D. R. Holmes, R. E. Vlietstra, H. C. Smith et al., "Restenosis after percutaneous transluminal coronary angioplasty (PTCA): a report from the PTCA registry of the national heart, lung, and blood institute," *The American Journal of Cardiology*, vol. 53, 1984.

[225] M. Nobuyoshi, T. Kimura, H. Nosaka et al., "Restenosis after successful percutaneous transluminal coronary angioplasty: serial angiographic follow-up of 229 patients," *Journal of the American College of Cardiology*, vol. 12, 1988.

[226] A. Grüntzig, "Transluminal dilatation of coronary-artery stenosis," *Lancet*, vol. 311, 1978.

[227] E. Eeckhout, L. Kappenberger, and J. J. Goy, "Stents for intracoronary placement: current status and future directions," *Journal of the American College of Cardiology*, vol. 27, 1996.

[228] G. S. Roubin, A. D. Cannon, S. K. Agrawal et al., "Intracoronary stenting for acute and threatened closure complicating percutaneous transluminal coronary angioplasty," *Circulation*, vol. 85, 1992.

[229] J. Iqbal, J. Gunn, and P. W. Serruys, "Coronary stents: historical development, current status and future directions," *British Medical Bulletin*, vol. 106, 2013.

[230] J. Y. Bang, U. Navaneethan, M. K. Hasan, B. Sutton, R. Hawes, and S. Varadarajulu, "Non-superiority of lumen-apposing metal stents over plastic stents for drainage of walled-off necrosis in a randomised trial," *Gut*, vol. 68, 2019.

[231] O. Varenne, S. Cook, G. Sideris et al., "Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial," *Lancet*, vol. 391, 2018.

[232] J. F. Iglesias, O. Muller, D. Heg et al., "Biodegradable polymer sirolimus-eluting stents versus durable polymer everolimus-eluting stents in patients with ST-segment elevation myocardial infarction (BIOSTEMI): a single-blind, prospective, randomised superiority trial," *Lancet*, vol. 394, no. 10205, pp. 1243–1253, 2019.

[233] A. J. Guerra, P. Cano, M. Rabionet, T. Puig, and J. Ciurana, "3D-printed PCL/PLA composite stents: towards a new solution to cardiovascular problems," *Materials*, vol. 11, 2018.